

(19)



Europäisches Patentamt

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(11)

**EP 0 995 751 B1**

(12)

**EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention  
of the grant of the patent:  
**29.06.2005 Bulletin 2005/26**

(51) Int Cl.<sup>7</sup>: **C07D 487/04**, A61K 31/506,  
C07D 231/14, C07D 401/12  
// (C07D487/04, 239:00,  
213:00)

(21) Application number: **99308158.7**

(22) Date of filing: **15.10.1999**

**(54) Pyrazolopyrimidinone cGMP PDE5 inhibitors for the treatment of sexual dysfunction**

Pyrazolopyrimidinone cGMP PDE5 Inhibitoren zur Behandlung der sexuellen Dysfunktion

Inhibiteurs de cGMP PDE5 de pyrazolopyrimidinone servant à traiter le dysfonctionnement sexuel

(84) Designated Contracting States:  
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU  
MC NL PT SE**

(30) Priority: **23.10.1998 GB 9823103**

(43) Date of publication of application:  
**26.04.2000 Bulletin 2000/17**

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**AT BE CH DE DK ES FI FR GR IE IT LI LU MC NL  
CY PT SE**  
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<b>EP-A- 0 636 626</b>	<b>EP-A- 0 812 845</b>
<b>WO-A-93/07149</b>	<b>WO-A-94/00453</b>
<b>WO-A-94/28902</b>	<b>WO-A-96/16657</b>
<b>WO-A-96/28429</b>	<b>WO-A-96/28448</b>
<b>WO-A-98/49166</b>	<b>WO-A-99/54333</b>

- **DUMAITRE B ET AL: "SYNTHESIS AND CYCLIC  
GMP PHOSPHODIESTERASE INHIBITORY  
ACTIVITY OF A SERIES OF  
6-PHENYLPYRAZOLO-  
3,4-DIHYDRO-PYRIMIDONES" JOURNAL OF  
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CHEMICAL SOCIETY. WASHINGTON, vol. 39, no.  
8, 1 January 1996 (1996-01-01), pages 1635-1644,  
XP002024856 ISSN: 0022-2623**
- **PATENT ABSTRACTS OF JAPAN vol. 1997, no.  
02, 28 February 1997 (1997-02-28) & JP 08 253484  
A (TAISHO PHARMACEUT CO LTD), 1 October  
1996 (1996-10-01)**
- **TERRETT N K ET AL: "Sildenafil (VIAGRA), a  
potent and selective inhibitor of type 5 CGMP  
phosphodiesterase with utility for the treatment  
of male erectile dysfunction" BIOORGANIC &  
MEDICINAL CHEMISTRY  
LETTERS,GB,OXFORD, vol. 6, no. 15, 6 August  
1996 (1996-08-06), pages 1819-1824,  
XP004135609 ISSN: 0960-894X**

Remarks:

The file contains technical information submitted  
after the application was filed and not included in this  
specification

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**EP 0 995 751 B1**

## Description

## Field of the Invention

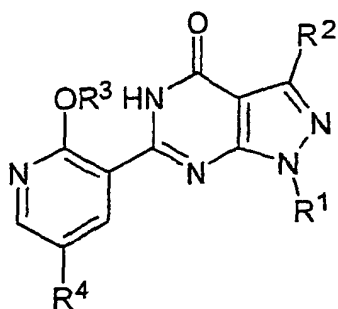
[0001] This invention relates to pharmaceutically useful compounds, in particular compounds which are useful in the inhibition of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs), such as type 5 cyclic guanosine 3',5'-monophosphate phosphodiesterase (cGMP PDE5). The compounds therefore have utility in a variety of therapeutic areas, including male erectile dysfunction (MED).

## Prior Art

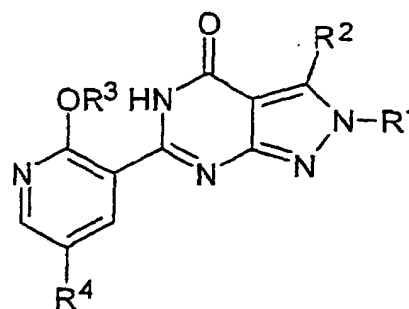
[0002] International patent application WO 93/07149 discloses certain pyrazolo[3,4-d]pyrimidinone compounds as antianginal agents. International patent application WO 96/16657 discloses the use of these compounds (amongst others) in the treatment of MED. International patent application WO 94/28902 discloses the use of certain pyrazolo-pyrimidinone compounds in the treatment of impotence. A process for the preparation of such compounds is disclosed in EP 0 812 845. International patent applications WO 98/49166 and WO 99/54333, published in 5 November 1998 and 28 October 1999, respectively, disclose the use of certain pyrazolo[4,3-d]pyrimidinone compounds in the treatment of impotence. Patent application numbers EP 0 636 626, WO 96/28448, WO 96/28429, and JP 08253484, as well as journal articles *J. Med. Chem.* 19, 1635 (1996) and *Bioorg. Med. Chem. Lett.* 6, 1819 (1996), disclose pyrazolo[3,4-d]pyrimidinone compounds that act as inhibitors of cGMP PDEs. Purinone compounds that inhibit cGMP PDEs are disclosed in WO 94/00453.

## Disclosure of the Invention

[0003] According to the invention there is provided compounds of formulae IA and IB:



IA



IB

wherein

R<sup>1</sup> represents linear or cyclic C<sub>2-5</sub> alkyl, Het or C<sub>1-3</sub> alkylHet, in which both latter cases, Het represents a six-membered aromatic ring containing one or two nitrogen atoms;

R<sup>2</sup> represents linear or branched, cyclic, acyclic or part-cyclic C<sub>1-4</sub> alkyl (which alkyl group is optionally terminated by OH), C<sub>1-3</sub> alkylHet (in which Het represents a six-membered heterocyclic group containing one or two nitrogen atoms), C<sub>1-3</sub> alkylaryl (the alkyl group of which is optionally interrupted by an O atom), aryl or Het (in which Het represents a six-membered heterocyclic group containing one or two nitrogen atoms);

R<sup>3</sup> represents linear or branched C<sub>1-6</sub> alkyl, optionally terminated by OH or O-methyl;

R<sup>4</sup> represents SO<sub>2</sub>NR<sup>12</sup>R<sup>13</sup>;

R<sup>12</sup> and R<sup>13</sup>, together with the nitrogen atom to which they are attached, represent

4-R<sup>14</sup>-piperazinyl, in which R<sup>14</sup> represents C<sub>1-6</sub> alkyl, optionally terminated by OH; and

R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10a</sup>, R<sup>10b</sup>, R<sup>11a</sup> and R<sup>11b</sup> independently represent H or C<sub>1-6</sub> alkyl; and

the term "aryl" means a six- to ten-membered carbocyclic aromatic group, which group is optionally substituted with one or more substituents selected from aryl, C<sub>1-6</sub> alkyl, Het, halo, cyano, nitro, OR<sup>5</sup>, C(O)R<sup>6</sup>, C(O)OR<sup>7</sup>, C(O)NR<sup>8</sup>R<sup>9</sup>, NR<sup>10a</sup>R<sup>10b</sup>, SO<sub>2</sub>NR<sup>11a</sup>R<sup>11b</sup> and N(H)SO<sub>2</sub>R<sup>11a</sup>;

or a pharmaceutically, or a veterinarily, acceptable salt or solvate thereof.

[0004] "Het" groups may be in the form of an N-oxide.

[0005] For the avoidance of doubt, the nitrogen atom to which R<sup>12</sup> and R<sup>13</sup> are attached is the nitrogen atom that must be present in the relevant piperazinyl group.

[0006] Alkyl groups which R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10a</sup>, R<sup>10b</sup>, R<sup>11a</sup>, R<sup>11b</sup> and R<sup>14</sup> may represent may, when there is a sufficient number of carbon atoms, be linear or branched, be saturated or unsaturated, be cyclic, acyclic or part cyclic/acyclic, be interrupted by oxygen and/or be substituted by one or more halo atom.

[0007] The alkyl groups of alkylHet and alkylaryl may, when there is a sufficient number of carbon atoms, be linear or branched, be saturated or unsaturated, and/or be interrupted by oxygen. When used in this context, the terms "Het" and "aryl" are as defined hereinbefore.

[0008] Halo groups with which aryl and above-mentioned alkyl groups may be substituted or terminated include fluoro, chloro bromo and iodo.

[0009] Pharmaceutically, and veterinarily, acceptable derivatives includes salts and solvates. Salts which may be mentioned include: acid addition salts, for example, salts formed with inorganic acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acid, with carboxylic acids or with organo-sulphonic acids; base addition salts; metal salts formed with bases, for example, the sodium and potassium salts. Pharmaceutically acceptable derivatives also include C<sub>1</sub> to C<sub>4</sub> alkyl ammonium salts.

[0010] Further preferred compounds of the invention include those wherein R<sup>1</sup> represents linear or cyclic C<sub>2-5</sub> alkyl and R<sup>2</sup> represents C<sub>1-4</sub> alkyl, Het, C<sub>1-3</sub> alkylHet, aryl or C<sub>1-3</sub> alkylaryl.

[0011] Preferred compounds of the invention include those wherein: R<sup>3</sup> represents linear or branched C<sub>1-4</sub> alkyl, optionally terminated by OH or O-methyl.

[0012] Particularly preferred compounds of the invention include those wherein:

R<sup>1</sup> represents ethyl, *n*-propyl or cyclopentyl, -CH<sub>2</sub>-Het (in which Het represents pyridin-2-yl) or pyrimidin-2-yl;  
 R<sup>2</sup> represents methyl, hydroxymethyl, ethyl, propyl or cyclopropylmethyl, -CH<sub>2</sub>Het (where Het is pyridin-2-yl, pyrimidin-2-yl, morpholinyl or pyrazin-2-yl), benzyl, -CH<sub>2</sub>OCH<sub>2</sub>-phenyl, phenyl or pyrazin-2-yl;  
 R<sup>3</sup> represents linear or branched C<sub>2-3</sub> alkyl, optionally terminated by OCH<sub>3</sub>;  
 R<sup>12</sup> and R<sup>13</sup>, together with the nitrogen atom to which they are attached, represent 4-R<sup>14</sup>-piperazinyl, in which R<sup>14</sup> represents C<sub>1-3</sub> alkyl optionally terminated by OH.

[0013] Most preferred compounds of the invention include the compounds of Examples 18 to 25 described herein-after.

[0014] The compounds of the invention may exhibit tautomerism. All tautomeric forms of the compounds of formulae IA and IB, and mixtures thereof, are included within the scope of the invention.

[0015] The compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques e.g. by fractional crystallisation or chromatography. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional techniques e.g. fractional crystallisation or HPLC. The desired optical isomers may be prepared by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation. Alternatively, the desired optical isomers may be prepared by resolution, either by HPLC of the racemate using a suitable chiral support or, where appropriate, by fractional crystallisation of the diastereoisomeric salts formed by reaction of the racemate with a suitable optically active acid or base. All stereoisomers are included within the scope of the invention.

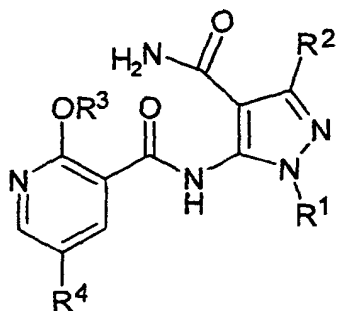
[0016] Also included within the scope of the invention are radiolabelled derivatives of compounds of formulae IA and IB which are suitable for biological studies.

## Preparation

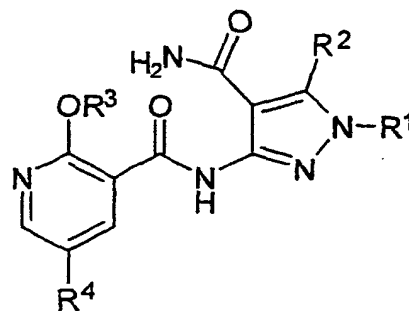
[0017] According to a further aspect of the invention there is provided processes for the preparation of compounds of the invention, as illustrated below.

[0018] The following processes are illustrative of the general synthetic procedures which may be adopted in order to obtain the compounds of the invention:

[0019] 1. Compounds of formulae IA and IB may be prepared by cyclisation of corresponding compounds of formulae IIA and IIB, respectively:



IIA

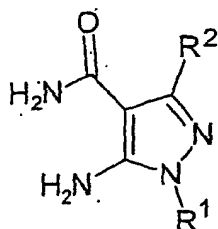


IIB

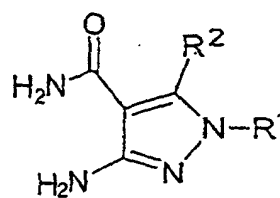
wherein  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are as defined previously for compounds of formulae IA and IB.

**[0020]** This cyclisation may be accomplished under basic, neutral or acidic conditions using known methods for pyrimidone ring formation. Preferably, the cyclisation is performed under basic conditions using an alkali metal salt of an alcohol or amine, such as sodium ethoxide, potassium tert-butoxide or potassium bis(trimethylsilyl) amide, in the presence of a suitable solvent, for example at reflux temperature (or, if performed in a sealed vessel, at greater than reflux temperature). The skilled person will appreciate that, when an alcohol is selected as solvent, an appropriate alcohol of formula  $R^3OH$ , or a sterically hindered alcohol, eg 3-methyl pentan-3-ol, may be used if it is intended to mitigate alkoxide exchange at either the 2-position of the pyridin-3-yl substituent.

**[0021]** Compounds of formulae IIA and IIB may be prepared by reaction of corresponding compounds of formulae IIIA and IIIB, respectively:

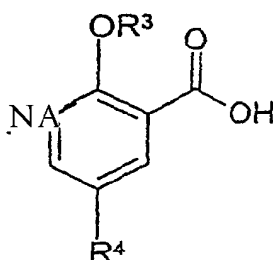


IIIA



IIIB

wherein  $R^1$  and  $R^2$  are as defined previously for compounds of formulae IIA and IIB, with a compound of formula IV or a carboxylic acid derivative thereof:



IV

wherein  $R^3$  and  $R^4$  are as defined previously for compounds of formula IIA and IIB.

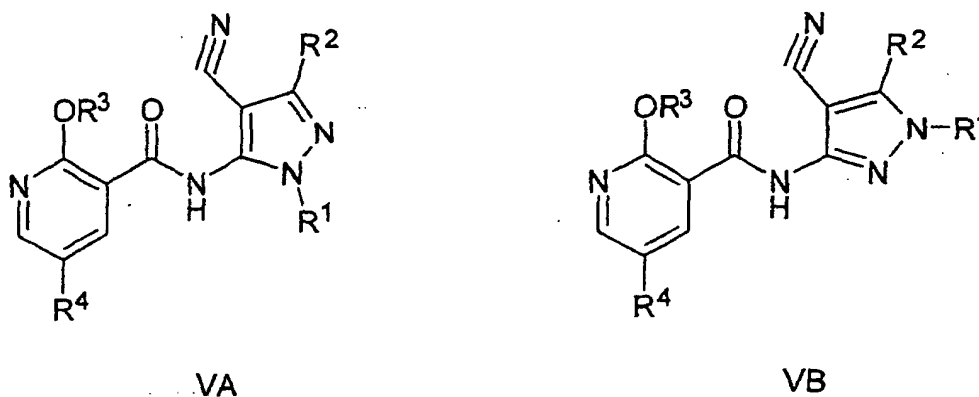
[0022] This coupling reaction may be achieved by conventional amide bond forming techniques which are well known to those skilled in the art. For example, an acyl halide (e.g. chloride) derivative of a compound of formula IV may be reacted with a compound of formula IIIA or IIIB in the presence of an excess of a tertiary amine, such as triethylamine or pyridine, optionally in the presence of a suitable catalyst, such as 4-dimethyl aminopyridine, in a suitable solvent such as dichloromethane, at a temperature of about 0°C to room temperature.

[0023] A variety of other amino acid coupling methodologies may be used to couple the compound of formula IIIA and IIIB with the compound of formula IV. For example, the acid of formula IV or a suitable salt thereof (eg sodium salt) may be activated with an appropriate activating reagent, e.g. a carbodiimide, such as 1,3-dicyclocarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride optionally in the presence of 1-hydroxybenzotriazole hydrate and/or a catalyst such as 4-dimethylaminopyridine; a halotrisaminophosphonium salt such as bromotris(pyrridiny)phosphonium hexafluorophosphate; or a suitable pyridinium salt such as 2-chloro-1-methyl pyridinium chloride. Either type of coupling reaction may be conducted in a suitable solvent such as dichloromethane or tetrahydrofuran, optionally in the presence of a tertiary amine such as N-methylmorpholine or N-ethyl-diisopropylamine (for example when either the compound of formula IIIA or IIIB, or the activating agent is presented in the form of an acid addition salt), at from about 0°C to about room temperature. Preferably, from about 1 to 2 molecular equivalents of the activating reagent and from 1 to 3 molecular equivalents of any tertiary amine present may be employed.

[0024] Alternatively, the carboxylic acid function of IV may be activated using an excess of a reagent such as N,N'-carbonyldiimidazole in an appropriate solvent, eg ethyl acetate, dichloromethane or butan-2-one, at from about room temperature to about 80°C, followed by reaction of the intermediate imidazolide with either a compound of the formula IIIA or IIIB at from about 20°C to about 90°C.

[0025] In a further variation, a compound of formula IA or IB, as defined previously, may be formed in a one-pot procedure by coupling a compound of formula IIIA or IIIB with the acyl chloride derivative of formula IV and by cyclising the resultant intermediate compound of formula IIA or IIB, using the methods as described previously. The one-pot procedure may further involve an *in-situ* coupling and cyclisation reaction to form a compound of formula IA or IB. Preferably, pyridine may serve as an acid scavenger and as the solvent for the *in-situ* coupling and cyclisation reaction.

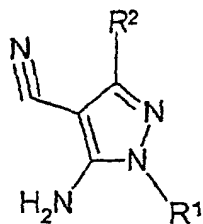
[0026] 2. Compounds of formulae IA and IB may be prepared by cyclisation of corresponding compounds of formulae VA and VB, respectively:



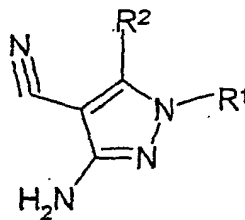
wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as defined previously for compounds of formulae IA and IB.

[0027] Preferably, the cyclisation is accomplished *via* hydrolysis, more preferably in the presence of a suitable base such as potassium hydroxide and a suitable solvent, such as a sterically hindered alcohol, such as 3-methyl-3-pentanol, for example at reflux temperature.

[0028] Compounds of formulae VA and VB may be prepared by reaction of corresponding compounds of formulae VIA and VIB, respectively:



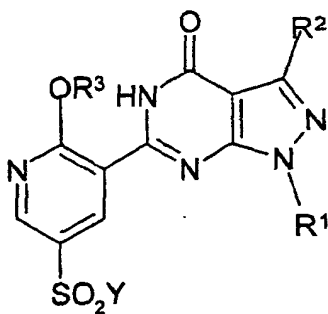
VIA



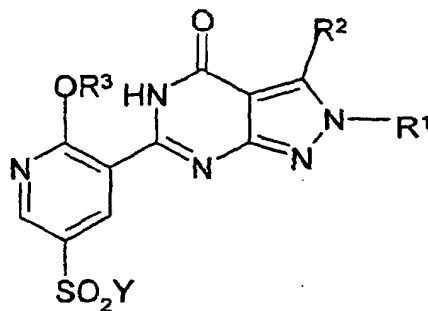
VIB

wherein  $R^1$  and  $R^2$  are as previously defined for compounds of formulae VA and VB, with a compound of formula IV or a carboxylic acid derivative thereof as defined previously, using standard amide bond forming techniques, for example as described hereinbefore in respect of the coupling of a compound of formula IIIA or IIIB with a compound of formula IV.

**[0029]** 3. Compounds of formulae IA and IB may be prepared by reaction of corresponding compounds of formulae VIIA and VIIB, respectively:

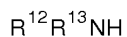


VIIA



VIIB

wherein Y is halo, preferably chloro, bromo or iodo,  $R^1$ ,  $R^2$  and  $R^3$  are as previously defined for compounds of formulae IA and IB, with a compound of formula VIII:

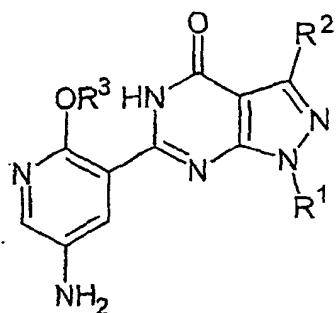


VIII

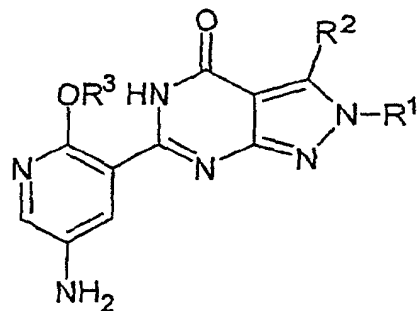
wherein  $R^{12}$  and  $R^{13}$  are as previously defined for compounds of formulae IA and IB.

**[0030]** This reaction is typically performed at  $0^\circ\text{C}$  to room temperature, preferably in the presence of an appropriate solvent such as a  $C_1$  to  $C_3$  alcohol or dichloromethane, optionally using an excess of the compound of formula VIII and, optionally, in the presence of another suitable base, such as triethylamine.

**[0031]** Compounds of formulae VIIA and VIIB may be prepared from corresponding compounds of formulae XVA and XVB, respectively:



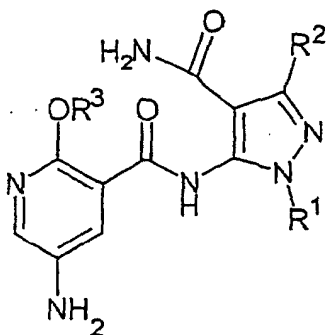
XVA



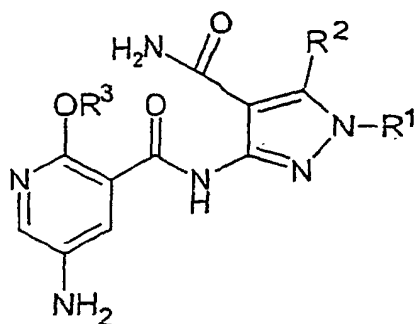
XVB

wherein  $R^1$ ,  $R^2$  and  $R^3$  are as previously defined for compounds of formulae VIIA and VIIB, for example using methods known to those skilled in the art for converting an amino group to an  $SO_2Y$  group (in which  $Y$  is as previously defined for compounds of formulae VIIA and VIIB). For example, compounds of formulae VIIA and VIIB in which  $Y$  is chloro may be prepared by reacting a corresponding compound of formula XVA or XVB with about a two-fold excess of sodium nitrite in a mixture of concentrated hydrochloric acid and glacial acetic acid, at from about  $-25^\circ\text{C}$  to about  $0^\circ\text{C}$ , followed by treatment with excess liquid sulphur dioxide and a solution of about a three-fold excess of cupric chloride in aqueous acetic acid, at from about  $-15^\circ\text{C}$  to about room temperature.

**[0032]** Compounds of formula XVA and XVB may be prepared by cyclisation of a corresponding compound of formula XVC or XVD (as appropriate):



XVC

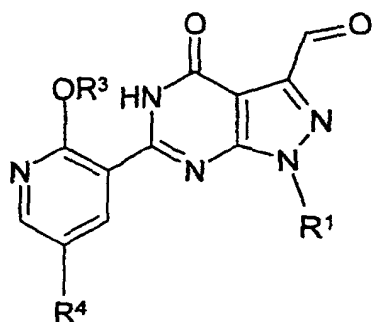


XVD

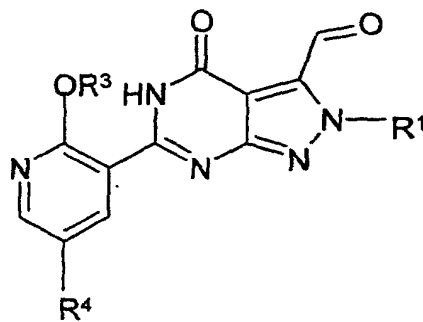
wherein  $R^1$ ,  $R^2$  and  $R^3$  are as hereinbefore defined for compounds of formulae XVA and XVB, for example under similar conditions to those described hereinbefore for preparation of compounds of formulae IA and IB.

**[0033]** Compounds of formulae XVA and XVB may alternatively be prepared by reduction of the corresponding nitro-pyridine compound under conditions which are well known to those skilled in the art. Such nitro compounds may be prepared by cyclisation of appropriate precursors, for example as described above.

**[0034]** 4. Compounds of formulae IA and IB, in which  $R^2$  represents  $C_{1-4}$  alkyl,  $C_{1-3}$  alkylHet or  $C_{1-3}$  alkylaryl, may alternatively be prepared by reaction of corresponding compounds of formulae XVIA and formula XVIB, respectively:



XVI A

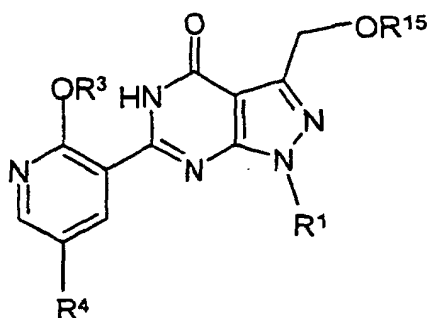


XVI B

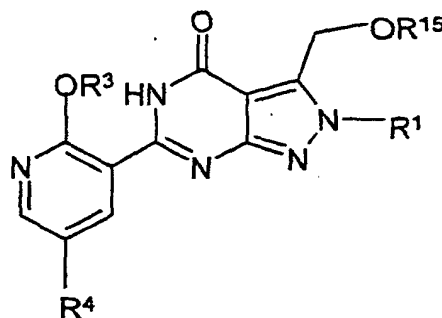
wherein  $R^1$ ,  $R^3$  and  $R^4$  are as previously defined for compounds of formulae IA and IB, with either an organometallic compound of formula  $R^{2a}M$  as hereinbefore defined, followed by deoxygenation of the resultant secondary alcohol, using methods which are well known to those skilled in the art, or by reductive amination using a basic compound which provides an  $R^2$  group upon reaction with the  $-C=O$  group which is attached to the pyrazole ring (e.g. a group which provides  $(R^{2a})^-$ , prior to reaction with the carbonyl, such a morpholinyl), using methods which are well known to those skilled in the art.

[0035] Compounds of formulae XVI A and XVI B may be prepared by oxidation of corresponding compounds of formulae IA or IB, in which  $R^2$  represents  $CH_2OH$  using methods which are well known to those skilled in the art.

[0036] 5. Compounds of formulae IA and IB in which  $R^2$  represents  $CH_2OH$  may be prepared by the deprotection of corresponding compounds of formulae XVII A and XVII B, respectively:



XVII A



XVII B

wherein  $R^1$ ,  $R^3$  and  $R^4$  are as previously defined for compounds of formulae IA and IB and  $R^{15}$  represents an alcohol protecting group, for example a benzyl group, using methods that are well known to those skilled in the art.

[0037] 6. Compounds of formulae IA and IB in which  $R^1$  represents  $C_{2-5}$  alkyl or  $C_{1-3}$  alkylHet may be prepared by alkylation of corresponding compounds of formulae IA and IB, respectively, in which  $R^1$  represents H, for example as described hereinbefore for preparation of compounds of formulae IX A and IX B.

[0038] Compounds of formulae III A and III B, IV, VIA and VIB, VIII, and XVC and XVD and derivatives thereof, when not commercially available or not subsequently described, may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from readily accessible starting materials using appropriate reagents and reaction conditions.

[0039] Substituents on the aryl and Het groups in the above-mentioned compounds may be introduced, and interconverted, using techniques which are well known to those skilled in the art.

[0040] The skilled person will also appreciate that various standard substituent or functional group interconversions and transformations within certain compounds of formulae IA and IB will provide other compounds of formulae IA and IB. Examples include alkoxide exchange at the 2-position of the pyridin-3-yl substituents, and for compounds in which  $R^2$  or  $R^3$  represents an alkyl group which is terminated by OH, deprotection of a corresponding ether compound of formula IA or IB (see the Examples below). Moreover, certain compounds of formulae IA and IB, for example those in which  $R^{12}$  and  $R^{13}$ , together with the nitrogen to which they are attached, form a 4- $R^{14}$ -piperazinyl group may be



prepared directly from the corresponding piperazine analogues in which R<sup>14</sup> is replaced by hydrogen, using standard procedures (e.g. alkylation).

[0041] The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

[0042] It will be appreciated by those skilled in the art that, in the course of carrying out the above processes described above, the functional groups of intermediate compounds may need to be protected by protecting groups.

[0043] Functional groups which it is desirable to protect include hydroxy, amino and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl and diarylalkylsilyl groups (e.g. *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl) and tetrahydropyranyl. Suitable protecting groups for amino include *tert*-butoxycarbonyl, 9-fluorenylmethoxycarbonyl or benzyloxycarbonyl. Suitable protecting groups for carboxylic acid include C<sub>1-6</sub> alkyl or benzyl esters.

[0044] The protection and deprotection of functional groups may take place before or after any of the reaction steps described hereinbefore.

[0045] Protecting groups may be removed in accordance with techniques which are well known to those skilled in the art.

[0046] The use of protecting groups is fully described in "Protective Groups in Organic Chemistry", edited by JWF McOmie, Plenum Press (1973), and "Protective Groups in Organic Synthesis", 2<sup>nd</sup> edition, TW Greene & PGM Wutz, Wiley-Interscience (1991).

[0047] Persons skilled in the art will also appreciate that, in order to obtain compounds of formula I in an alternative, and, on some occasions, more convenient, manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or chemical transformations performed upon, different intermediates to those mentioned hereinbefore in conjunction with a particular reaction). This will depend *inter alia* on factors such as the nature of other functional groups present in a particular substrate, the availability of key intermediates and the protecting group strategy (if any) to be adopted. Clearly, the type of chemistry involved will influence the choice of reagent that is used in the said synthetic steps, the need, and type, of protecting groups that are employed, and the sequence for accomplishing the synthesis.

[0048] Pharmaceutically acceptable acid addition salts of the compounds of formulae IA and IB which contain a basic centre may be prepared in a conventional manner. For example, a solution of the free base may be treated with the appropriate acid, either neat or in a suitable solvent, and the resulting salt may then be isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts can be obtained in an analogous manner by treating a solution of a compound of formula IA or IB with the appropriate base. Both types of salt may be formed or interconverted using ion-exchange resin techniques.

[0049] It will be appreciated by those skilled in the art that certain protected derivatives of compounds of formula I, which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". Further, certain compounds of formula I may act as prodrugs of other compounds of formula I.

## Medical Use

[0050] The compounds of the invention are useful because they possess pharmacological activity in animals, especially mammals, including humans. They are therefore indicated as pharmaceuticals, as well as for use as animal medicaments.

[0051] According to a further aspect of the invention there is provided the compounds of the invention for use as pharmaceuticals, and for use as animal medicaments.

[0052] In particular, compounds of the invention have been found to be potent and selective inhibitors of cGMP PDEs, such as cGMP PDE5, for example as demonstrated in the tests described below, and are thus useful in the treatment of medical conditions in humans, and in animals, in which cGMP PDEs, such as cGMP PDE5, are indicated, and in which inhibition of cGMP PDEs, such as cGMP PDE5, is desirable.

[0053] By the term "treatment", we include both therapeutic (curative) or prophylactic treatment.

[0054] Thus, according to a further aspect of the invention there is provided the use of the compounds of the invention in the manufacture of a medicament for the treatment of a medical condition in which a cGMP PDE (e.g. cGMP PDE5) is indicated. There is further provided the use of the compounds of the invention in the manufacture of a medicament for the treatment of a medical condition in which inhibition of a cGMP PDE (e.g. cGMP PDE5) is desirable.

[0055] The compounds of the invention are thus expected to be useful for the curative or prophylactic treatment of male erectile dysfunction (MED), female sexual dysfunction (FSD), premature labour, dysmenorrhoea, benign prostatic hyperplasia (BPH), bladder outlet obstruction, incontinence, stable and unstable variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, con-

ditions of reduced blood vessel patency (e.g. post transluminal coronary angioplasty (post-PTCA)), chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma and diseases characterised by disorders of gut motility (e.g. irritable bowel syndrome (IBS)). Other conditions which may be mentioned include pre-eclampsia, Kawasaki's syndrome, nitrate tolerance, multiple sclerosis, peripheral diabetic neuropathy, stroke, Alzheimer's disease, acute respiratory failure, psoriasis, skin necrosis, cancer metastasis, baldness, nutcracker oesophagus, anal fissure and hypoxic vasoconstriction. Particularly preferred conditions include MED and FSD.

**[0056]** Thus, the invention provides the use of the compounds of the invention in a method of treating or preventing a medical condition for which a cGMP PDE5 inhibitor is indicated, in an animal (e.g. a mammal, including a human being), which comprises administering a therapeutically effective amount of a compound of the invention to a mammal in need of such treatment.

## Pharmaceutical Preparations

**[0057]** The compounds of the invention will normally be administered orally or by any parenteral route, in the form of pharmaceutical preparations comprising the active ingredient, optionally in the form of a non-toxic organic, or inorganic, acid, or base, addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated, as well as the route of administration, the compositions may be administered at varying doses.

**[0058]** The compounds of the invention may also be combined with any other drugs useful in the inhibition of cGMP-PDEs, such as cGMP-PDE5.

**[0059]** In human therapy, the compounds of the invention can be administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

**[0060]** For example, the compounds of the invention can be administered orally, buccally or sublingually in the form of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed- or controlled-release applications. The compounds of invention may also be administered via intracavernosal injection.

**[0061]** Such tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycolate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

**[0062]** Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compounds of the invention may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

**[0063]** The compounds of the invention can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion techniques. They are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

**[0064]** For oral and parenteral administration to human patients, the daily dosage level of the compounds of the invention will usually be from 10 to 500 mg/kg (in single or divided doses).

**[0065]** Thus, for example, the tablets or capsules of the compound of the invention may contain from 5 mg to 250 mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention.

**[0066]** The compounds of the invention can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray or nebuliser with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A™ or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA™), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the pro-

pellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

**[0067]** Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 1 to 50 mg of a compound of the invention for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 1 to 50 mg, which may be administered in a single dose or, more usually, in divided doses throughout the day.

**[0068]** Alternatively, the compounds of the invention can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. The compounds of the invention may also be transdermally administered, for example, by the use of a skin patch. They may also be administered by the ocular route, particularly for treating diseases of the eye.

**[0069]** For ophthalmic use, the compounds of the invention can be formulated as micronised suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

**[0070]** For application topically to the skin, the compounds of the invention can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetaryl alcohol, 2-octyldodecanol, benzyl alcohol and water.

**[0071]** The skilled person will also be appreciated that, in the treatment of certain conditions (including MED and FSD), compounds of the invention may be taken as a single dose on an "as required" basis (i.e. as needed or desired).

**[0072]** Generally, in humans, oral administration of the compounds of the invention is the preferred route, being the most convenient and, for example in MED, in avoiding the well-known disadvantages associated with intracavernosal (i.c.) administration.

**[0073]** A preferred oral dosing regimen in MED for a typical man is from 25 to 250 mg of compound when required.

**[0074]** In circumstances where the recipient suffers from a swallowing disorder or from impairment of drug absorption after oral administration, the drug may be administered parenterally, e.g. sublingually or buccally.

**[0075]** For veterinary use, a compound of the invention is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular animal.

**[0076]** Thus, according to a further aspect of the invention there is provided a pharmaceutical formulation including a compound of the invention in admixture with a pharmaceutically or veterinarily acceptable adjuvant, diluent or carrier.

**[0077]** In addition to the fact that compounds of the invention inhibit cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs) and in particular, are potent and selective inhibitors of cGMP PDE5, compounds of the invention may also have the advantage that they may be more efficacious than, be less toxic than, have a broader range of activity than, be more potent than, produce fewer side effects than, be more easily absorbed than, or they may have other useful pharmacological properties over, compounds known in the prior art.

**[0078]** The biological activities of the compounds of the present invention were determined by the following test methods.

## Biological Tests

### *Phosphodiesterase (PDE) Inhibitory Activity*

**[0079]** *In vitro* PDE inhibitory activities against cyclic guanosine 3',5'-monophosphate (cGMP) and cyclic adenosine 3',5'-monophosphate (cAMP) phosphodiesterases were determined by measurement of their  $IC_{50}$  values (the concentration of compound required for 50% inhibition of enzyme activity).

**[0080]** The required PDE enzymes were isolated from a variety of sources, including human corpus cavernosum, human and rabbit platelets, human cardiac ventricle, human skeletal muscle and bovine retina, essentially by the method of W.J. Thompson and M.M. Appleman (Biochem., 1971, 10, 311). In particular, the cGMP-specific PDE (PDE5) and the cGMP-inhibited cAMP PDE (PDE3) were obtained from human corpus cavernosum tissue, human platelets or rabbit platelets; the cGMP-stimulated PDE (PDE2) was obtained from human corpus cavernosum; the calcium/calmodulin (Ca/CAM)-dependent PDE (PDE1) from human cardiac ventricle; the cAMP-specific PDE (PDE4) from human skeletal muscle; and the photoreceptor PDE (PDE6) from bovine retina.

**[0081]** Assays were performed using a modification of the "batch" method of W.J. Thompson *et al.* (Biochem., 1979, 18, 5228). Results from these tests show that the compounds of the present invention are potent and selective inhibitors

of cGMP-specific PDE5.

#### *Functional Activity*

[0082] This was assessed *in vitro* by determining the capacity of a compound of the invention to enhance sodium nitroprusside-induced relaxation of precontracted rabbit corpus cavernosum tissue strips, as described by S.A. Ballard *et al.* (Brit. J. Pharmacol., 1996, 118 (suppl.), abstract 153P).

#### *In Vivo Activity*

[0083] Compounds may be screened in anaesthetised dogs to determine their capacity, after i.v. administration, to enhance the pressure rises in the corpora cavernosa of the penis induced by intracavernosal injection of sodium nitroprusside, using a method based on that described by Trigo-Rocha *et al.* (Neurourol. and Urodyn., 1994, 13, 71).

#### *Safety Profile*

[0084] Compounds of the invention may be tested at varying i.v and p.o. doses in animals such as mouse and dog, observing for any untoward effects.

### **Examples and Preparations**

[0085] The synthesis of the compounds of the invention and of the intermediates for use therein are illustrated by the following Examples and Preparations.

[0086] <sup>1</sup>H nuclear magnetic resonance (NMR) spectra were recorded using either a Varian Unity 300 or a Varian Inova 400 spectrometer and were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: eg s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

[0087] Mass spectra (m/z) were recorded using a Fisons Instruments Trio mass spectrometer in the thermospray ionisation mode.

[0088] Room temperature includes 20 to 25°C.

[0089] Where any of the following examples do not fall within the scope of the accompanying claims, it is to be understood that they are disclosed for the purposes of understanding the invention, and are thus provided in an illustrative sense.

#### Synthesis of Intermediates

##### Preparation 1

##### 2-(1-Hydroxy-2-phenylethylidene)malononitrile

[0090] A solution of malononitrile (4.0g, 60mmol) in tetrahydrofuran (25ml), was added dropwise over an hour to an ice-cooled suspension of sodium hydride (4.80g, 60%, 120mmol) in tetrahydrofuran (75ml), and the mixture stirred at room temperature for an hour, and then re-cooled to 0°C. A solution of phenylacetyl chloride (8.0ml, 60mmol) in tetrahydrofuran (20ml) was added dropwise over an hour, maintaining the temperature below 10°C, and the reaction mixture then stirred at room temperature for 36 hours. Water (10ml) was added, the mixture concentrated under reduced pressure, the residue partitioned between ether (50ml), and 1N hydrochloric acid (50ml) and the phases separated. The aqueous layer was extracted with ether (2x50ml), the combined organic layers washed with brine (50ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was dissolved in acetonitrile (100ml), filtered to remove residual silicon oil, and the filtrate evaporated under reduced pressure, to afford the title compound as a brown oil, (11.20g). δ (CDCl<sub>3</sub>) : 3.93 (2H, s), 7.30 (2H, m), 7.40 (3H, m).

##### Preparation 2

##### 2-[2-(Benzyloxy)-1-hydroxyethylidene]malononitrile

[0091] Obtained as a beige solid (33%), after recrystallisation from diisopropyl ether, from benzyloxyacetyl chloride and malononitrile, using a similar procedure to that described in preparation 1. δ (CDCl<sub>3</sub>) : 4.46 (2H, s), 4.72 (2H, s), 7.34 (2H, m), 7.41 (3H, m).

Preparation 32-(1-Hydroxy-2-methylpropylidene)malononitrile

**[0092]** Obtained as a beige solid (88%) from isobutyryl chloride and malononitrile using the procedure of preparation 1.

$\delta$  (CDCl<sub>3</sub>): 1.23 (6H, d), 3.16 (1H, m).

Preparation 42-(2-Cyclopropyl-1-hydroxyethylidene)malononitrile

**[0093]** Obtained as a brown oil (100%) from cyclopropylacetyl chloride (J.Med.Chem. 1984, 27, 1291) and malononitrile, using the procedure of preparation 1.

$\delta$  (CDCl<sub>3</sub>): 0.34 (2H, m), 0.63 (2H, m), 1.05 (1H, m), 2.53 (2H, d), 9.72 (1H, s).

LRMS : m/z 166 (M+18)<sup>+</sup>

Preparation 52-(1-Methoxy-2-phenylethylidene)malononitrile

**[0094]** A solution of the title compound of preparation 1 (11.20g, 62mmol) in tetrahydrofuran (50ml) was added dropwise to an ice cooled solution of sodium hydride (5.86g, 60%, 62mmol) in tetrahydrofuran (40ml) and the mixture stirred at room temperature for 20 minutes, then re-cooled to 0°C in an ice bath. A solution of dimethyl sulphate (2.48g, 62mmol) in tetrahydrofuran (40ml) was added dropwise over an hour and once addition was complete the reaction was heated under reflux for 3 hours, then stirred for a further 18 hours at room temperature. The reaction mixture was concentrated under reduced pressure, the residue partitioned between ethyl acetate (100ml) and ice cold sodium hydrogen carbonate solution (50ml), and the phases separated. The organic layer was washed with water (25ml), brine (25ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel, using an elution gradient of ether:pentane (95:5 to 50:50) to afford the title compound as an orange oil, (7.47g).

$\delta$  (CDCl<sub>3</sub>) : 4.02 (5H, m), 7.22-7.42 (5H, m).

Preparation 62-[2-(Benzyloxy)-1-methoxyethylidene]malononitrile

**[0095]** Obtained as a brown oil (78%) from the title compound of preparation 2, using a similar procedure to that described in preparation 5.

$\delta$  (CDCl<sub>3</sub>) : 3.98 (3H, s), 4.20 (2H, s), 4.43 (2H, s), 7.38 (5H, m).

Preparation 72-(1-Methoxy-2-methylpropylidene)malononitrile

**[0096]** A solution of the title compound of preparation 3 (3.37g, 24.8mmol) in dioxan (25ml) was added to a suspension of sodium hydride (780mg, 26mmol) in dioxan (40ml), the mixture stirred for 10 minutes, and dimethyl sulphate (2.5ml, 26mmol) added dropwise. The reaction mixture was heated under reflux for 18 hours, cooled and concentrated under reduced pressure. The residue was partitioned between ethyl acetate (100ml) and water (50ml), the phases separated, and the organic layer washed with brine (25ml), dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel, using dichloromethane as eluant to afford the title compound as a pale yellow oil, (2.62g).

$\delta$  (CDCl<sub>3</sub>) : 1.20 (6H, d), 3.19 (1H, m), 4.38 (3H, s).

LRMS : m/z 168 (M+18)<sup>+</sup>

Preparation 82-(2-Cyclopropyl-1-methoxyethylidene)malononitrile

**[0097]** Obtained as an oil (45%) from the title compound of preparation 4, using a similar procedure to that described in preparation 5.

$\delta$  (CDCl<sub>3</sub>) : 0.38 (2H, m), 0.62 (2H, m), 0.98 (1H, m), 2.58 (2H, d), 4.17 (3H, s).

LRMS : m/z 180 (M+18)<sup>+</sup>

Preparation 95-Amino-3-benzyl-1-n-propyl-1H-pyrazole-4-carbonitrile

**[0098]** A mixture of propyl hydrazine oxalate (5.0g, 30mmol) and sodium methoxide (3.46g, 60mmol) in methanol (50ml) was stirred at room temperature for 2 hours. A solution of the title compound of preparation 5 (6.03g, 30mmol) in methanol (10ml) was added dropwise, and the reaction mixture heated under reflux for 4 hours. The cooled mixture was concentrated under reduced pressure, the residue suspended in a dichloromethane:methanol (90:10) (100ml) solution and filtered. The filtrate was evaporated under reduced pressure and the crude product purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol (100:0 to 95:5) to afford the title compound as a yellow solid, (5.13g).

$\delta$  (CDCl<sub>3</sub>) : 0.95 (3H, t), 1.80 (2H, m), 3.78 (2H, t), 4.20 (2H, s), 7.18-7.34 (5H, m).

LRMS : m/z 241 (M+1)<sup>+</sup>

Preparation 105-Amino-3-(benzyloxy)methyl-1-n-propyl-1H-pyrazole-4-carbonitrile

**[0099]** Sodium methoxide (7.2g, 132mmol) was added portionwise to a suspension of propyl hydrazine hydrochloride (7.3g, 66mmol) in methanol (100ml) and the mixture stirred for 10 minutes. A solution of the title compound of preparation 6 (15.0g, 66mmol) in methanol (50ml) was added dropwise over an hour, and once addition was complete, the reaction mixture was heated under reflux for 4 hours, and a further 18 hours at room temperature. Water (2ml) was added, the mixture concentrated under reduced pressure and the residue partitioned between ethyl acetate (100ml), and brine (100ml), and the phases separated. The aqueous layer was extracted with ethyl acetate (2x100ml), the combined organic layers dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol (98:2 to 94:6) to afford the title compound, (3.7g).

$\delta$  (CDCl<sub>3</sub>) : 0.88 (3H, t), 1.80 (2H, m), 3.88 (2H, t), 4.50 (2H, s), 4.55 (2H, s), 7.36 (5H, m).

LRMS : m/z 271 (M+1)<sup>+</sup>

Preparation 115-Amino-3-(benzyloxy)methyl-1-ethyl-1H-pyrazole-4-carbonitrile

**[0100]** Obtained as a pale yellow oil (37%) from the title compound of preparation 6, and ethyl hydrazine oxalate using the procedure of preparation 10.

LRMS : m/z 258 (M+ 1)<sup>+</sup>

Preparation 125-Amino-3-isopropyl-1-n-propyl-1H-pyrazole-4-carbonitrile

**[0101]** Obtained as a yellow powder (6%) from the title compound of preparation 7 and propyl hydrazine hydrochloride, using the procedure of preparation 10.

$\delta$  (CDCl<sub>3</sub>) : 0.97 (3H, t), 1.32 (6H, d), 1.82 (2H, m), 2.98 (1H, m), 3.80 (2H, t), 4.10 (2H, s).

Preparation 135-Amino-3-cyclopropylmethyl-1-n-propyl-1H-pyrazole-4-carbonitrile

5 **[0102]** Obtained as a yellow solid (40%) from the title compound of preparation 8 and propyl hydrazine oxalate, using the procedure of preparation 9.

$\delta$  (CDCl<sub>3</sub>) : 0.22 (2H, m), 0.50 (2H, m), 0.92 (3H, t), 1.02 (1H, m), 1.80 (2H, m), 2.47 (2H, d), 3.78 (2H, t), 4.10 (2H, s).  
LRMS : m/z 205 (M+1)<sup>+</sup>

10 Preparation 145-Amino-1-ethyl-3-(2-pyrazinyl)-1H-pyrazole-4-carbonitrile

15 **[0103]** Sodium hydride (9.72g, 60%, 243mmol) was added portionwise to a cooled (5°C) solution of malononitrile (7.9g, 120mmol) in tetrahydrofuran (75ml), and the mixture stirred for 20 minutes. A solution of 2-pyrazinecarbonyl chloride (J.Med.Chem. 1992, 35, 1214) (17.1g, 120mmol) in tetrahydrofuran (250ml) was added dropwise so as to maintain the internal temperature below 10°C, and the mixture then stirred at room temperature for an hour. Dimethyl sulphate (18.16g, 144mmol) was added, the mixture heated under reflux for 3 hours, allowed to cool, triethylamine (58.5ml, 420mmol) and ethyl hydrazine oxalate (18g, 120mmol) added and the reaction mixture heated under reflux  
20 for 18 hours. The solvent was decanted from the cooled reaction mixture and the residual brown gum extracted with dichloromethane (2x150ml). The combined organic solutions were evaporated under reduced pressure and the crude product purified by column chromatography on silica gel, using ethyl acetate:hexane (50:50) as eluant to afford the title compound, (1.2g).

$\delta$  (CDCl<sub>3</sub>) : 1.48 (3H, t), 4.03 (2H, q), 4.35 (2H, s), 8.50 (1H, s), 8.61 (1H, s), 9.17 (1H, s).

25 LRMS : m/z 215 (M+1)<sup>+</sup>

Preparation 155-Amino-1-n-propyl-3-(2-pyrazinyl)-1H-pyrazole-4-carbonitrile

30 **[0104]** Obtained as a solid (5%) from malononitrile, propyl hydrazine hydrochloride and 2-pyrazinecarbonyl chloride, using a similar procedure to that described in preparation 14.

$\delta$  (CDCl<sub>3</sub>) : 1.02 (3H, t), 1.94 (2H, m), 3.97 (2H, t), 4.37 (2H, s), 8.55 (1H, s), 8.65 (1H, s), 9.20 (1H, s).

35 LRMS : m/z 229 (M+1)<sup>+</sup>

Preparation 165-Amino-1-ethyl-3-phenyl-1H-pyrazole-4-carbonitrile

40 **[0105]** Obtained (23%) from benzoyl chloride, malononitrile and ethyl hydrazine oxalate using a similar procedure to that described in preparation 14.  $\delta$  (CDCl<sub>3</sub>) : 1.42 (3H, t), 3.98 (2H, q), 4.22 (2H, s), 7.37 (3H, m), 7.87 (2H, d).

LRMS : m/z 213 (M+1)<sup>+</sup>

Preparation 17

45 **[0106]** A mixture of the title compound of preparation 9 (1.80g, 7.50mmol) and sodium hydroxide (900mg, 22.5mmol) in ethanol (15ml) and water (15ml), was heated under reflux for 24 hours. The cooled reaction mixture was filtered and the solid dried under suction to afford the title compound as a white solid, (1.18g).

$\delta$  (DMSO-d<sub>6</sub>) : 0.86 (3H, t), 1.68 (2H, m), 3.80 (2H, t), 4.02 (2H, s), 6.18 (2H, s), 6.33 (2H, s), 7.18 (3H, m), 7.26 (2H, m).  
LRMS : m/z 259 (M+1)<sup>+</sup>

Preparation 18

55 **[0107]** Obtained as a solid (77%) from the title compound of preparation 11, using the procedure of preparation 17.

5-Amino-3-(benzyloxy)methyl-1-ethyl-1H-pyrazole-4-carboxamide

**[0107]** Obtained as a solid (77%) from the title compound of preparation 11, using the procedure of preparation 17.

LRMS : m/z 275 (M + 1)<sup>+</sup>

#### Preparation 19

##### 5 5-Amino-3-(benzyloxy)methyl-1-n-propyl-1H-pyrazole-4-carboxamide

**[0108]** Obtained as white crystals (90%), from the title compound of preparation 10, using the procedure of preparation 17.

$\delta$  (CDCl<sub>3</sub>) : 0.84 (3H, t), 1.75 (2H, m), 3.80 (2H, t), 4.58 (2H, s), 4.63 (2H, s), 4.85 (2H, s), 7.34 (5H, m).

10

#### Preparation 20

##### 5-Amino-3-isopropyl-1-n-propyl-1H-pyrazole-4-carboxamide

15 **[0109]** A mixture of the title compound of preparation 12 (834mg, 4.3mmol) and aqueous sodium hydroxide (13ml, 1N, 13mmol) in ethanol (15ml) was heated under reflux for 72 hours. The cooled reaction mixture was partitioned between ethyl acetate (20ml) and water (15ml) and the phases separated. The aqueous layer was acidified to pH 6 with 2N hydrochloric acid and extracted with ethyl acetate (3x20ml). These combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residual yellow oil was purified by column chromatography on silica gel, using an elution gradient of ether:hexane (35:65 to 100:0) to afford the title compound as a pale yellow solid, (260mg).

20

$\delta$  (CDCl<sub>3</sub>) : 0.98 (3H, t), 1.37 (6H, d), 1.81 (2H, m), 2.99 (1H, m), 3.80 (2H, t), 5.29 (2H, s), 5.37 (2H, s).

LRMS : m/z 211 (M+1)<sup>+</sup>

25

#### Preparation 21

##### 5-Amino-3-cyclobutylmethyl-1-n-propyl-1H-pyrazole-4-carboxamide

30 **[0110]** Obtained as a solid (42%) from the title compound of preparation 13, using a similar procedure to that described in preparation 20, but using an elution gradient of dichloromethane: isopropanol (100:0 to 90:10).

$\delta$  (CDCl<sub>3</sub>) : 0.21 (2H, m), 0.50 (2H, m), 0.92 (3H, t), 1.04 (1H, m), 1.78 (2H, m), 2.70 (2H, d), 3.77 (2H, t), 5.23 (2H, s), 5.50 (2H, s).

LRMS : m/z 223 (M + 1)<sup>+</sup>

35

#### Preparation 22

##### 5-Amino-1-ethyl-3-(2-pyrazinyl)-1H-pyrazole-4-carboxamide

40 **[0111]** A mixture of the title compound of preparation 14 (1.1g, 5.1mmol) and sodium hydroxide (617mg, 15.4mmol) in water (10ml) and ethanol (10ml) was heated under reflux for 24 hours and the cooled reaction mixture evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of ethyl acetate:hexane:ethanol (50:50:0 to 90:0:10) to afford the title compound as a white solid, (695mg).

$\delta$  (CDCl<sub>3</sub>) : 1.49 (3H, t), 4.02 (2H, q), 5.44 (1H, s), 5.74 (2H, s), 8.42 (1H, s), 8.55 (1H, s), 9.50 (1H, s), 10.43 (1H, s).

LRMS : m/z 233 (M + 1)<sup>+</sup>

45

#### Preparation 23

##### 5-Amino-1-n-propyl-3-(2-pyrazinyl)-1H-pyrazole-4-carboxamide

50 **[0112]** Obtained as a solid (38%) from the title compound of preparation 15, using the procedure of preparation 22.

$\delta$  (CDCl<sub>3</sub>) : 1.01 (3H, t), 1.94 (2H, m), 3.96 (2H, t), 5.42 (1H, s), 5.70 (2H, s), 8.42 (1H, s), 8.55 (1H, s), 9.48 (1H, s), 10.44 (1H, s).

LRMS : m/z 247 (M+1)<sup>+</sup>

55



Preparation 245-Amino-1-ethyl-3-phenyl-1H-pyrazole-4-carboxamide

**[0113]** A mixture of the title compound of preparation 16 (1.75g, 8.3mmol) and sodium hydroxide (990mg, 24.8mmol) in water (25ml) and ethanol (25ml) was heated under reflux for 24 hours. The cooled reaction mixture was concentrated under reduced pressure to remove the ethanol, and the residual aqueous solution extracted with dichloromethane (3x25ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of ethyl acetate:hexane (50:50 to 100:0) to afford the title compound, (460mg).  
 $\delta$  (CDCl<sub>3</sub>) : 1.40 (3H, t), 3.96 (2H, q), 5.15 (2H, s), 5.37 (2H, s), 7.41 (3H, m), 7.52 (2H, d).  
 LRMS : m/z 231 (M + 1)<sup>+</sup>

Preparation 253-[(Benzyloxy)methyl]-5-(2-n-propoxybenzamido)-1-n-propyl-1H-pyrazole-4-carboxamide

**[0114]** A solution of 2-n-propoxybenzoyl chloride (1.98g, 10mmol) in dichloromethane (30ml) was added to a cooled solution of the title compound of preparation 19 (2.88g, 10mmol) and triethylamine (2.02g, 20mmol) in dichloromethane (30ml) and the reaction stirred for 90 minutes. The reaction mixture was concentrated under reduced pressure, the residue suspended in ethyl acetate (200ml), washed consecutively with water (50ml), 2N sodium hydroxide solution (50ml), 2N hydrochloric acid (50ml) and brine (50ml), dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of hexane:ethyl acetate (100:0 to 0:100) to afford the title compound as a white solid, (3.17g).  
 $\delta$  (CDCl<sub>3</sub>) : 0.84 (3H, t), 1.00 (3H, t), 1.80 (2H, m), 1.94 (2H, m), 4.00 (2H, t), 4.19 (2H, t), 4.58 (2H, s), 4.75 (2H, s), 6.98 (1H, d), 7.02 (1H, m), 7.32 (5H, m), 7.41 (1H, m), 8.21 (1H, d), 10.87 (1H, s).

Preparation 263-[(Benzyloxy)methyl]-6-(2-n-propoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0115]** A mixture of the title compound of preparation 25 (2.93g, 6.5mmol) and potassium t-butoxide (900mg, 8.0mmol) in isopropanol (50ml) was heated under reflux for 5 hours, then cooled. The reaction mixture was diluted with ethyl acetate (100ml), washed with ammonium chloride solution (50ml) and brine (50ml), dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was recrystallised from ether, to afford the title compound, (2.90g).  
 $\delta$  (CDCl<sub>3</sub>) : 0.92 (3H, t), 1.16 (3H, t), 1.98 (4H, m), 4.17 (2H, t), 4.22 (2H, t), 4.58 (2H, s), 5.01 (2H, s), 7.00 (1H, d), 7.10 (1H, m), 7.29 (5H, m), 7.44 (1H, m), 8.60 (1H, d), 10.96 (1H, s).

Preparation 273-Methyl-6-(2-n-propoxyphenyl)-1H-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0116]** 2-n-Propoxybenzoyl chloride (12.2g, 61mmol) was added slowly to an ice cold suspension of 5-amino-4-cyano-3-methyl-1H-pyrazole (J. Med. Chem. 1996, 39, 1639) (5.0g, 41mmol) in pyridine (20ml) and the reaction stirred at room temperature for an hour. Water (3ml) was added, the mixture concentrated under reduced pressure and the residue partitioned between water (20ml) and ethyl acetate (50ml). The phases were separated, the organic layer dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure and azeotroped with toluene to give a yellow solid. 30% Sodium peroxide solution (32ml) was added slowly to a mixture of the intermediate amide, and sodium hydroxide solution (400ml, 1N, 400mmol) in ethanol (300ml) and the reaction heated under reflux for 18 hours. The cooled reaction mixture was concentrated under reduced pressure, the residual aqueous solution acidified to pH 6 using hydrochloric acid, and the resulting precipitate filtered, washed with water and ether and dried under suction. This beige solid was purified by column chromatography on silica gel, using an elution gradient of ethyl acetate:hexane (20:80 to 50:50) and recrystallised from methanol to afford the title compound. (2.0g).  
 $\delta$  (CDCl<sub>3</sub>) : 1.18 (3H, t), 2.02 (2H, m), 2.64 (3H, s), 4.20 (2H, t), 7.06 (1H, d), 7.26 (1H, m), 7.52 (1H, m), 8.43 (1H, d), 10.06 (1H, s), 11.08 (1H, s).  
 LRMS : m/z 285 (M+1)<sup>+</sup>

Preparation 283-Methyl-6-(2-n-propoxyphenyl)-1-(pyridin-2-yl)methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

[0117] and

Preparation 293-Methyl-6-(2-n-propoxyphenyl)-2-(pyridin-2-yl)methyl-2,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

[0118] Sodium hydride (78mg, 60%, 2.6mmol) was added to an ice cooled solution of the title compound of preparation 27 (205mg, 0.7mmol) in tetrahydrofuran (15ml) and the mixture stirred for 30 minutes. 2-Chloromethyl pyridine (prepared from 576mg, 2.2mmol of the hydrochloride) in tetrahydrofuran (5ml) was added and the reaction stirred at 50°C for 48 hours and a further 72 hours at room temperature. Methanol (2ml) was added and the reaction mixture evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of hexane:isopropanol:0.88 ammonia (90:10:0.75 to 80:20:1.5) and repeated using ethyl acetate:hexane (80:20 to 100:0) to afford the title compound of preparation 28, (85mg)

$\delta$  (CDCl<sub>3</sub>) : 1.20 (3H, t), 2.02 (2H, m), 2.63 (3H, s), 4.20 (2H, t), 5.70 (2H, s), 6.99-7.20 (4H, m), 7.48 (1H, m), 7.60 (1H, m), 8.46 (1H, d), 8.60 (1H, s), 11.10 (1H, s).

LRMS : m/z 376 (M + 1)<sup>+</sup>

followed by the title compound of preparation 29, (210mg).

$\delta$  (CDCl<sub>3</sub>) : 1.14 (3H, t), 1.98 (2H, m), 2.69 (3H, s), 4.16 (2H, t), 5.50 (2H, s), 6.99-7.20 (4H, m), 7.42 (1H, m), 7.60 (1H, m), 8.54 (1H, d), 8.58 (1H, d), 10.85 (1H, d).

LRMS : m/z 376 (M+1)<sup>+</sup>

Preparation 303-Methyl-6-(2-n-propoxyphenyl)-2-(pyrimidin-2-yl)-2,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

[0119] Obtained as a solid (39%) from the title compound of preparation 27 and 2-bromopyrimidine, using a similar procedure to that described in preparation 29, but using ethyl acetate:hexane:ethanol (50:50:0 to 95:0:5) as chromatographic eluant.

$\delta$  (CDCl<sub>3</sub>) : 1.18 (3H, t), 2.00 (2H, m), 3.13 (3H, s), 4.18 (2H, t), 7.02 (1H, d), 7.12 (1H, m), 7.30 (1H, m), 7.46 (1H, m), 8.62 (1H, d), 8.85 (2H, d), 10.91 (1H, s).

LRMS : m/z 363 (M+1)<sup>+</sup>

Preparation 313-Hydroxymethyl-6-(2-n-propoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

[0120] A mixture of the title compound of preparation 26 (1.19g, 2.75mmol) and 10% palladium on charcoal (1.0g) in industrial methylated spirits (IMS; 40ml) was hydrogenated at 50psi and 50°C for 72 hours. The reaction mixture was filtered, the filter pad washed well with IMS and the combined filtrate evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of ethyl acetate:hexane (0: 100 to 100:0) to afford the title compound as a white solid (615mg).

$\delta$  (CDCl<sub>3</sub>) : 0.94 (3H, t), 1.16 (3H, t), 1.98 (4H, m), 4.16 (4H, m), 4.94 (2H, d), 5.62 (1H, m), 7.02 (1H, d), 7.12 (1H, m), 7.45 (1H, m), 8.60 (1H, d), 11.14 (1H, s).

Preparation 324-Oxo-6-(2-n-propoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-3-carbaldehyde

[0121] N-Methylmorpholine oxide (390mg, 3.33mmol), followed by tetrapropylammonium perruthenate (30mg; 0.09mmol) were added to a mixture of the title compound of preparation 31 (569mg, 1.66mmol) and 4Å molecular sieves (750mg) in acetonitrile (10ml) and dichloromethane (10ml), and the reaction stirred at room temperature for 18 hours. The reaction mixture was filtered, the filtrate diluted with ethyl acetate (50ml), washed with 0.5N hydrochloric acid (20ml), then brine (20ml), dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using ethyl acetate as eluant, to afford the title compound as a white crystalline

solid, (367mg).

$\delta$  (CDCl<sub>3</sub>) : 0.98 (3H, t), 1.20 (3H, t), 2.00 (4H, m), 4.22 (2H, t), 4.70 (2H, t), 7.06 (1H, d), 7.18 (1H, m), 7.51 (1H, m), 8.62 (1H, d), 10.48 (1H, s), 11.30 (1H, s).

#### 5 Preparation 33

##### 3-[Hydroxy-(pyridin-2-yl)methyl]-6-(2-n-propoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0122]** n-Butyl lithium (2.5ml, 1.6M in hexane, 4mmol) was added dropwise to a cooled (-78°C) solution of 2-bromopyridine (632mg, 4mmol) in tetrahydrofuran (10ml) and the mixture stirred for 10 minutes. A solution of the title compound of preparation 32 (340mg, 1mmol) in tetrahydrofuran (5ml) was added and the reaction stirred for 30 minutes. 2N hydrochloric acid (4ml) was added, the mixture allowed to warm to room temperature, basified with 2N sodium hydroxide solution, and extracted with ethyl acetate (3x20ml). The combined organic extracts were washed with brine (20ml), dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of hexane:ethyl acetate (100:0 to 0:100) to afford the title compound as an oil, (246mg).  
 $\delta$  (CDCl<sub>3</sub>) : 0.93 (3H, t), 1.14 (3H, t), 1.21 (1H, d), 1.98 (4H, m), 4.13 (2H, m), 4.34 (1H, m), 4.49 (1H, m), 6.18 (1H, d), 6.97-7.24 (3H, m), 7.41 (1H, m), 7.64 (2H, m), 8.41 (1H, s), 8.59 (1H, m), 11.15 (1H, s).  
 LRMS : m/z 420 (M+1)<sup>+</sup>

#### 20 Preparation 34

##### 3-[Hydroxy-(pyrimidin-2-yl)methyl]-6-(2-n-propoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0123]** n-Butyl lithium (6.6ml, 2.5M in hexane, 16.5mmol) was added dropwise to a cooled (-78°C) solution of tri-n-butyl-stannyl-2-pyrimidine (Tetrahedron, 1994, 50, 275) (6.06g, 16.4mmol) in tetrahydrofuran (50ml), so as to maintain the internal temperature below -68°C, and the mixture stirred for 15 minutes. A solution of the title compound of preparation 32 (1.86g, 5.47mmol) in tetrahydrofuran (50ml) was added dropwise over 20 minutes, and the reaction stirred for a further 30 minutes. Saturated ammonium chloride solution (50ml) was added, the mixture allowed to warm to room temperature, and diluted with ethyl acetate (100ml). The layers were separated, the organic layer washed with brine (50ml), dried (MgSO<sub>4</sub>), and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol (100:0 to 95:5) and triturated with ether, to afford the title compound as a crystalline solid, (450mg).  
 $\delta$  (CDCl<sub>3</sub>) : 0.92 (3H, t), 1.14 (3H, t), 1.98 (4H, m), 4.16 (2H, t), 4.28 (1H, m), 4.45 (1H, m), 6.21 (1H, d), 7.00 (1H, d), 7.08 (1H, m), 7.18 (1H, m), 7.32 (1H, d), 7.43 (1H, m), 8.60 (1H, d), 8.70 (1H, s), 11.14 (1H, s).  
 LRMS : m/z 421 (M+1)<sup>+</sup>

#### Preparation 35

##### O-[[4-oxo-6-(2-n-propoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-3-yl]](2-pyridinyl)methyl] 1H-imidazole-1-carbothioate

**[0124]** A mixture of the title compound of preparation 33 (210mg, 0.5mmol), and thiocarbonyldiimidazole (534mg, 3mmol) in dichloromethane (10ml) was stirred at room temperature for 5 days. The reaction mixture was purified directly by column chromatography on silica gel, using an elution gradient of hexane:ethyl acetate (100:0 to 0:100) to afford the title compound, (180mg).  
 $\delta$  (CDCl<sub>3</sub>) : 1.00 (3H, t), 1.16 (3H, t), 1.95-2.16 (4H, m), 4.18 (2H, t), 4.60 (2H, m), 7.07 (4H, m), 7.46 (1H, m), 7.77 (1H, m), 7.93 (1H, s), 7.99 (1H, d), 8.10 (1H, s), 8.52-8.68 (3H, m), 10.98 (1H, s).

#### Preparation 36

##### O-[[4-oxo-6-(2-n-propoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-3-yl]](2-pyrimidinyl)methyl] 1H-imidazole-1-carbothioate

**[0125]** A mixture of the title compound of preparation 34 (420mg, 1.0mmol) and thiocarbonyldiimidazole (890mg, 5.0mmol) in dichloromethane (10ml) was stirred at room temperature for 24 hours. The reaction mixture was poured into water (20ml), the layers separated, and the aqueous phase extracted with dichloromethane (3x40ml). The combined organic extracts were dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of hexane:ethyl acetate (100:0 to 0:100) to afford the

title compound as a yellow oil, (469mg).

$\delta$  (CDCl<sub>3</sub>) : 0.84 (3H, t), 1.12 (3H, t), 1.97 (4H, m), 4.11 (2H, t), 4.38 (2H, t), 6.99-7.10 (4H, m), 7.25 (1H, m), 7.42 (1H, m), 7.78 (1H, s), 8.37 (1H, s), 8.60 (1H, d), 8.72 (2H, m), 10.99 (1H, s).

LRMS : m/z 531 (M+1)<sup>+</sup>

#### Preparation 37

##### 6-(2-n-Propoxyphenyl)-1-n-propyl-3-(pyridin-2-yl)methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0126]** A solution of the title compound of preparation 35 (180mg, 0.34mmol) in toluene (10ml) was added dropwise to a solution of tri-n-butyltin hydride (291mg, 1mmol) in toluene (10ml) under reflux, over 30 minutes and the reaction heated for a further 3 hours under reflux. The cooled reaction mixture was purified directly by column chromatography on silica gel, using an elution gradient of hexane:ethyl acetate (100:0 to 0:100) to afford the title compound as a yellow gum, (32mg).

$\delta$  (CDCl<sub>3</sub>) : 0.84 (3H, t), 1.14 (3H, t), 1.84 (2H, m), 1.98 (2H, m), 4.15 (2H, t), 4.25 (2H, t), 4.63 (2H, s), 7.00 (1H, d), 7.10 (2H, m), 7.40 (2H, m), 7.57 (1H, m), 8.45 (1H, d), 8.60 (1H, d), 10.98 (1H, s).

LRMS : m/z 404 (M+1)<sup>+</sup>

#### Preparation 38

##### 6-(2-n-Propoxyphenyl)-1-n-propyl-3-(pyrimidin-2-yl)methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0127]** Obtained (32%) from the title compound of preparation 36, using a similar procedure to that described in preparation 37, except that an elution gradient of dichloromethane:methanol (100:0 to 96:4) was used as chromatographic eluant.

$\delta$  (CDCl<sub>3</sub>) : 0.81 (3H, t), 1.12 (3H, t), 1.84 (2H, m), 1.94 (2H, m), 4.12 (4H, m), 4.83 (2H, s), 6.99 (1H, d), 7.06 (1H, m), 7.13 (1H, m), 7.40 (1H, m), 8.59 (1H, d), 8.62 (2H, m), 10.85 (1H, s).

LRMS : m/z 405 (M + 1)<sup>+</sup>

#### Preparation 39

##### 2-Ethoxy-5-[4-(2-hydroxymethyl)piperazin-1-ylsulphonyl]benzoic acid

**[0128]** N-(2-hydroxyethyl)piperazine (3.40ml, 28.0mmol) was added to a solution of 2-ethoxy-5-chlorosulphonyl-benzoic acid (EP 812845 A1) (3.67g, 14.0mmol) in ethanol (25ml) and the reaction mixture stirred at room temperature for 72 hours. The reaction mixture was concentrated under reduced pressure, the residue suspended in water, acidified to pH 6, and extracted with dichloromethane (3x50ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residual brown oil was purified by column chromatography on reverse phase polystyrene resin using an elution gradient of water:acetonitrile (100:0 to 80:20) then triturated with acetonitrile to afford the title compound as a white solid, (1.10g).

$\delta$  (DMSO-d<sub>6</sub>) : 1.37 (3H, t), 2.38 (2H, t), 2.48 (4H, m), 2.84 (4H, m), 3.42 (2H, t), 4.20 (2H, q), 7.35 (1H, d), 7.80 (1H, d), 7.88 (1H, s).

LRMS : m/z 359 (M+1)<sup>+</sup>

#### Preparation 40

##### 2-Ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)benzoic acid chloride hydrochloride

**[0129]** Oxalyl chloride (11.7ml, 134mmol) was added dropwise to an ice cold suspension of 2-ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)benzoic acid (EP 812845 A1) (20.0g, 60.9mmol) and dimethylformamide (2 drops) in dichloromethane (200ml) over 15 minutes, and the reaction mixture stirred at room temperature for 18 hours. The mixture was concentrated under reduced pressure, the residue triturated with ether then ethyl acetate and dried at 40°C for 16 hours, to afford the title compound, (19.6g).

$\delta$  (DMSO-d<sub>6</sub>) : 1.35 (3H, t), 2.70 (5H, m), 3.12 (2H, m), 3.41 (2H, m), 3.75 (2H, m), 4.21 (2H, q), 7.38 (1H, d), 7.83 (1H, d), 7.94 (1H, s), 11.26 (1H, s).

Preparation 412-Ethoxy-5-[4-(2-hydroxyethyl)piperazin-1-ylsulphonyl]benzoic acid chloride hydrochloride

**[0130]** Oxalyl chloride (340ml, 2.79mmol) was added dropwise to an ice cold suspension of the title compound of preparation 39 (500mg, 1.40mmol) and dimethylformamide (2 drops) in dichloromethane (5ml), and the reaction stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure and azeotroped with toluene to afford the title compound as a white foam, (500mg).

LRMS : m/z 373 (M-Cl+OMe)<sup>+</sup>

Preparation 423-Benzyl-5-[5-(4-methylpiperazin-1-ylsulphonyl)-2-ethoxyphenyl]-carbonylamino-1-n-propyl-1H-pyrazole-4-carbonitrile

**[0131]** The title compound of preparation 40 (1.14g, 3.32mmol) was added to a suspension of the title compound of preparation 9 (360mg, 1.50mmol) in pyridine (5ml) and the reaction stirred at 70°C for 20 hours. The cooled reaction mixture was concentrated under reduced pressure, azeotroped with toluene, and the residual oil was partitioned between dichloromethane (10ml) and sodium bicarbonate solution (20ml). The phases were separated, the aqueous layer extracted with dichloromethane (2x15ml), and the combined organic solutions, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel, using an elution gradient of ethyl acetate:methanol (100:0 to 90:10) to afford the title compound as an off-white solid, (460mg).

δ (CDCl<sub>3</sub>) : 0.94 (3H, t), 1.62 (3H, t), 1.90 (2H, m), 2.25 (3H, s), 2.46 (4H, m), 3.05 (4H, m), 3.98 (2H, t), 4.04 (2H, s), 4.40 (2H, q), 7.17 (1H, d), 7.20-7.38 (5H, m), 7.92 (1H, d), 8.59 (1H, s), 9.59 (1H, s).

LRMS : m/z 551 (M+1)<sup>+</sup>

Preparation 433-Benzyl-5-[5-[4-(2-hydroxyethyl)piperazin-1-ylsulphonyl]-(2-ethoxy)phenyl]carbonylamino-1-n-propyl-1H-pyrazole-4-carboxamide

**[0132]** A mixture of the title compounds of preparations 17 (361mg, 1.40mmol) and 41 (527mg, 1.40mmol) in pyridine (5ml) was heated at 70°C for 20 hours. The cooled reaction mixture was concentrated under reduced pressure, azeotroped with toluene and the residual oil partitioned between dichloromethane (10ml) and sodium bicarbonate solution (20ml). The phases were separated, the aqueous layer extracted with dichloromethane (2x20ml), the combined organic solutions dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The crude product was triturated with ether to afford the title compound as a light brown solid, (477mg).

LRMS : m/z 599 (M+1)<sup>+</sup>

Preparation 445-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)phenyl]carbonylamino-1-ethyl-3-phenyl-1H-pyrazole-4-carboxamide

**[0133]** The title compound of preparation 24 (230mg, 1.0mmol) was added to the title compound of preparation 40 (383mg, 1.0mmol) in pyridine (6ml), and the reaction stirred at 60°C for 18 hours. The cooled reaction mixture was concentrated under reduced pressure and azeotroped with toluene. The residual yellow foam was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol (95:5 to 92:8) to afford the title compound, (180mg).

δ (CDCl<sub>3</sub>) : 1.52 (3H, t), 1.64 (3H, t), 2.22 (3H, s), 2.43 (4H, m), 3.02 (4H, m), 4.18 (2H, q), 4.42 (2H, q), 5.17 (1H, s), 5.43 (1H, s), 7.15 (1H, d), 7.42 (3H, m), 7.60 (2H, m), 7.87 (1H, d), 8.61 (1H, s), 10.72 (1H, s).

Preparation 453-[(Benzyloxy)methyl]-5-[2-ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)-phenyl]carbonylamino-1-n-propyl-1H-pyrazole-4-carboxamide

**[0134]** Obtained as a crystalline solid (47%) from the title compounds of preparations 19 and 40, using the procedure of preparation 43.

$\delta$  (CDCl<sub>3</sub>) : 0.86 (3H, t), 1.57 (3H, t), 1.81 (2H, m), 2.24 (3H, s), 2.44 (4H, m), 3.05 (4H, m), 4.01 (2H, t), 4.44 (2H, q), 4.59 (2H, s), 4.70 (2H, s), 7.08 (1H, d), 7.36 (5H, m), 7.82 (1H, d), 8.63 (1H, s), 11.32 (1H, s).

#### Preparation 46

#### 5-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)phenyl]carbonylamino-3-methyl-1-n-propyl-1H-pyrazole-4-carboxamide

**[0135]** Obtained as a brown foam, from the title compound of preparation 40 and 5-amino-3-methyl-1-n-propyl-3-pyrazole carboxamide (WO 9307149 A1), using the procedure described in preparation 44.

$\delta$  (CDCl<sub>3</sub>) : 0.93 (3H, t), 1.62 (2H, m), 1.90 (2H, m), 2.26 (3H, s), 2.45 (4H, m), 3.07 (4H, m), 4.00 (2H, t), 4.41 (2H, q), 7.15 (1H, d), 7.90 (1H, d), 8.61 (1H, s), 10.44 (1H, s).

LRMS : m/z 493 (M+1)<sup>+</sup>

#### Preparation 47

#### Pyridine-2-amino-5-sulphonic acid

**[0136]** 2-Aminopyridine (80g, 0.85mol) was added portionwise over 30 minutes to oleum (320g) and the resulting solution heated at 140°C for 4 hours. On cooling, the reaction was poured onto ice (200g) and the mixture stirred in an ice/salt bath for a further 2 hours. The resulting suspension was filtered, the solid washed with ice water (200ml) and cold IMS (200ml) and dried under suction to afford the title compound as a solid, (111.3g).

LRMS : m/z 175 (M+1)<sup>+</sup>

#### Preparation 48

#### Pyridine-2-amino-3-bromo-5-sulphonic acid

**[0137]** Bromine (99g, 0.62mol) was added dropwise over an hour, to a hot solution of the title compound of preparation 47 (108g, 0.62mol) in water (600ml) so as to maintain a steady reflux. Once the addition was complete the reaction was cooled and the resulting mixture filtered. The solid was washed with water and dried under suction to afford the title compound, (53.4g).

$\delta$  (DMSO-d<sub>6</sub>) : 8.08 (1H, s), 8.14 (1H, s). LRMS : m/z 253 (M)<sup>+</sup>

#### Preparation 49

#### Pyridine-3-bromo-2-chloro-5-sulphonyl chloride

**[0138]** A solution of sodium nitrite (7.6g, 110mmol) in water (30ml) was added dropwise to an ice-cooled solution of the title compound of preparation 48 (25.3g, 100mmol) in aqueous hydrochloric acid (115ml, 20%), so as to maintain the temperature below 6°C. The reaction was stirred for 30 minutes at 0°C and a further hour at room temperature. The reaction mixture was evaporated under reduced pressure and the residue dried under vacuum at 70°C for 72 hours. A mixture of this solid, phosphorus pentachloride (30g, 144mmol) and phosphorus oxychloride (1ml) was heated at 125°C for 3 hours, and then cooled. The reaction mixture was poured onto ice (100g) and the resulting solid filtered, and washed with water. The product was dissolved in dichloromethane, dried (MgSO<sub>4</sub>), filtered and evaporated under reduced pressure to afford the title compound as a yellow solid, (26.6g).

$\delta$  (CDCl<sub>3</sub>) : 8.46 (1H, s), 8.92 (1H, s).

#### Preparation 50

#### Pyridine-3-bromo-5-(4-ethylpiperazin-1-ylsulphonyl)-2-chloride

**[0139]** A solution of 1-ethyl piperazine (11.3ml, 89mmol) and triethylamine (12.5ml, 89mmol) in dichloromethane (150ml) was added dropwise to an ice-cooled solution of the title compound of preparation 49 (23g, 79mmol) in dichloromethane (150ml) and the reaction stirred at 0°C for an hour. The reaction mixture was concentrated under reduced pressure and the residual brown oil was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol (99:1 to 97:3) to afford the title compound as an orange solid, (14.5g).

$\delta$  (CDCl<sub>3</sub>) : 1.05 (3H, t), 2.42 (2H, q), 2.55 (4H, m), 3.12 (4H, m), 8.24 (1H, s), 8.67 (1H, s).

Preparation 513-Bromo-2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridine

**[0140]** A mixture of the title compound of preparation 50 (6.60g, 17.9mmol) and sodium ethoxide (6.09g, 89.55mmol) in ethanol (100ml) was heated under reflux for 18 hours, then cooled. The reaction mixture was concentrated under reduced pressure, the residue partitioned between water (100ml) and ethyl acetate (100ml), and the layers separated. The aqueous phase was extracted with ethyl acetate (2x100ml), the combined organic solutions dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to afford the title compound as a brown solid, (6.41g).

Found : C, 41.27; H, 5.33; N, 11.11. C<sub>13</sub>H<sub>20</sub>BrN<sub>3</sub>O<sub>3</sub>S requires C, 41.35; H, 5.28; N, 10.99%.

δ (CDCl<sub>3</sub>) : 1.06 (3H, t), 1.48 (2H, m), 2.42 (2H, q), 2.56 (4H, m), 3.09 (4H, m), 4.54 (2H, q), 8.10 (1H, s), 8.46 (1H, s). LRMS : m/z 380 (M+2)<sup>+</sup>

Preparation 52Pyridine-2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)-3-carboxylic acid ethyl ester

**[0141]** A mixture of the title compound of preparation 51 (6.40g, 16.92mmol), triethylamine (12ml), and palladium (0) tris(triphenylphosphine) in ethanol (60ml) was heated at 100°C and 200psi, under a carbon monoxide atmosphere, for 18 hours, then cooled. The reaction mixture was evaporated under reduced pressure and the residue purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol (100:0 to 97:3) to afford the title compound as an orange oil, (6.2g).

δ (CDCl<sub>3</sub>) : 1.02 (3H, t), 1.39 (3H, t), 1.45 (3H, t), 2.40 (2H, q), 2.54 (4H, m), 3.08 (4H, m), 4.38 (2H, q), 4.55 (2H, q), 8.37 (1H, s), 8.62 (1H, s). LRMS : m/z 372 (M + 1)<sup>+</sup>

Preparation 53Pyridine-2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)-3-carboxylic acid

**[0142]** A mixture of the title compound of preparation 52 (4.96g, 13.35mmol) and aqueous sodium hydroxide solution (25ml, 2N) in ethanol (25ml) was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure to half its volume, washed with ether and acidified to pH 5 using 4N hydrochloric acid. The aqueous solution was extracted with dichloromethane (3x30ml), the combined organic extracts dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to afford the title compound as a tan coloured solid, (4.02g).

δ (DMSO-d<sub>6</sub>) : 1.18 (3H, t), 1.37 (3H, t), 3.08 (2H, q), 3.17-3.35 (8H, m), 4.52 (2H, q), 8.30 (1H, s), 8.70 (1H, s).

Preparation 54Pyridine-2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)-3-carboxylic acid chloride hydrochloride

**[0143]** Oxalyl chloride (0.77ml, 8.85mmol) was added dropwise to an ice-cooled solution of the title compound of preparation 53 (1.52g, 4.42mmol) and dimethylformamide (2 drops) in dichloromethane (30ml) and the reaction stirred for 18 hours at room temperature. The mixture was concentrated under reduced pressure and the residue triturated with ethyl acetate. The resulting solid was filtered, washed with ether and dried under suction to afford the title compound (1.68g).

Found : C, 41.51; H, 5.27; N, 10.32. C<sub>14</sub>H<sub>21</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>4</sub>S; 0.10CH<sub>2</sub>Cl<sub>2</sub> requires C, 41.73; H, 5.02; N, 10.36%.

δ (CDCl<sub>3</sub>) : 1.46 (6H, m), 2.95 (2H, q), 3.11 (2H, m), 3.48 (2H, m), 3.55 (2H, m), 3.92 (2H, m), 4.60 (2H, q), 8.58 (1H, s), 8.66 (1H, s), 13.16 (1H, s).

Preparation 555-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]carbonylamino-1-ethyl-3-(pyrazin-2-yl)-1H-pyrazole-4-carboxamide

**[0144]** The title compound of preparation 22 (174mg, 0.75mmol) was added to a suspension of the title compound of preparation 54 (300mg, 0.75mmol) in pyridine (6ml), and the reaction stirred at 60°C for 18 hours. The cooled reaction mixture was concentrated under reduced pressure and azeotroped with toluene. The residue was purified by column chromatography on silica gel, using an elution gradient of methanol:ethyl acetate:dichloromethane (5:95:0 to 10:90:0)

to 10:0:90) to afford the title compound, (170mg).

$\delta$  (CDCl<sub>3</sub>) : 1.04 (3H, t), 1.60 (6H, m), 2.41 (2H, q), 2.57 (4H, m), 3.14 (4H, m), 4.24 (2H, q), 4.80 (2H, q), 5.60 (1H, s), 8.45 (1H, s), 8.60 (1H, s), 8.72 (1H, s), 8.82 (1H, s), 9.57 (1H, s), 10.57 (1H, s), 11.48 (1H, s).

LRMS : m/z 558 (M+1)<sup>+</sup>

#### Preparation 56

#### 5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]carbonyl-amino-1-n-propyl-3-(pyrazin-2-yl)-1H-pyrazole-4-carboxamide

**[0145]** Obtained (34%) from the title compounds of preparations 23 and 54, using the procedure described in preparation 55.

$\delta$  (CDCl<sub>3</sub>) : 1.00 (6H, m), 1.60 (3H, t), 2.02 (2H, m), 2.41 (2H, q), 2.55 (4H, m), 3.10 (4H, m), 4.18 (2H, t), 4.80 (2H, q), 5.60 (1H, s), 8.46 (1H, s), 8.60 (1H, s), 8.75 (1H, s), 8.83 (1H, s), 9.55 (1H, s), 10.56 (1H, s), 11.45 (1H, s).

LRMS : m/z 572 (M+1)<sup>+</sup>

#### Preparation 57

#### 5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]carbonylamino-1-ethyl-3-phenyl-1H-pyrazole-4-carboxamide

**[0146]** The title compound of preparation 24 (200mg, 0.9mmol) was added to a suspension of the title compound of preparation 54 (346mg, 0.9mmol) in pyridine (6ml) and the reaction stirred at 60°C for 72 hours. The cooled reaction mixture was concentrated under reduced pressure, azeotroped with toluene, and the residue partitioned between ethyl acetate (30ml) and water (15ml). The phases were separated, the organic layer dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of ethyl acetate:methanol (98:2 to 90:10) to afford the title compound, (70mg).

$\delta$  (CDCl<sub>3</sub>) : 1.01 (3H, t), 1.56 (6H, m), 2.40 (2H, m), 2.55 (4H, m), 3.13 (4H, m), 4.48 (2H, q), 4.75 (2H, q), 7.38 (1H, m), 7.43 (2H, m), 8.39 (2H, d), 8.66 (1H, s), 9.07 (1H, s), 10.78 (1H, s).

LRMS m/z: 556 (M+1)<sup>+</sup>

#### Preparation 58

#### 3-[(Benzyloxy)methyl]-5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]carbonylamino-1-ethyl-1H-pyrazole-4-carboxamide

**[0147]** A solution of the title compound of preparation 54 (4.14g, 10mmol) in dichloromethane (50ml) was added dropwise to an ice cold solution of the title compound of preparation 18 (2.74g, 10mmol) and triethylamine (2.02g, 20mmol) in dichloromethane (50ml), and the reaction stirred at room temperature for 16 hours. The reaction mixture was concentrated under reduced pressure, the residue partitioned between ether (50ml) and 1N citric acid solution (20ml), and the phases separated. The organic layer was extracted with 1N citric acid (2x20ml) and the aqueous solutions extracted with dichloromethane (3x60ml). The combined dichloromethane extracts were dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol (100:0 to 95:5), then repeated using ethyl acetate:methanol (100:0 to 85:15), to afford the title compound as a clear gum, (944mg).

$\delta$  (CDCl<sub>3</sub>) : 1.00 (3H, t), 1.46 (3H, t), 1.58 (3H, t), 2.39 (2H, q), 2.50 (4H, m), 3.04 (4H, m), 4.10 (2H, q), 4.53 (2H, s), 4.70 (2H, s), 4.78 (2H, q), 5.22 (1H, s), 7.29 (5H, m), 7.79 (1H, s), 8.65 (1H, s), 8.80 (1H, s), 11.04 (1H, s).

LRMS : m/z 600 (M+1)<sup>+</sup>

#### Preparation 59

#### 6-[2-Ethoxy-5-[(4-methylpiperazin-1-ylsulphonyl)phenyl]-3-(hydroxymethyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0148]** 10% Palladium on charcoal (1.7g) was added portionwise to an ice cold suspension of the title compound of example 9 (1.20g, 2.07mmol) in methanol (50ml) and then formic acid (5ml) added dropwise. The mixture was heated under reflux for 6 hours, under a nitrogen atmosphere, then cooled. Palladium acetate (200mg, 0.89mmol), triphenylphosphine (460mg, 1.7mmol) and formic acid (5ml) were added and the mixture heated under reflux for a further 8



hours. The cooled reaction mixture was filtered, the filtrate concentrated under reduced pressure and the residue partitioned between dichloromethane (40ml) and saturated sodium bicarbonate solution (15ml). The phases were separated, the organic layer dried ( $\text{Na}_2\text{SO}_4$ ), evaporated under reduced pressure and the residue triturated with ether, to afford the title compound, (240mg).

Found : C, 53.66; H, 6.16; N, 16.79.  $\text{C}_{22}\text{H}_{30}\text{N}_6\text{O}_5\text{S}$  requires C, 53.86; H, 6.17; N, 17.13%.

$\delta$  ( $\text{CDCl}_3$ ) : 1.00 (3H, t), 1.65 (3H, t), 2.00 (2H, m), 2.25 (3H, s), 2.48 (4H, m), 3.10 (4H, m), 4.20 (2H, t), 4.40 (2H, q), 5.00 (2H, s), 5.50 (1H, s), 7.18 (1H, d), 7.86 (1H, d), 8.99 (1H, s), 10.82 (1H, s). LRMS : m/z 491 ( $\text{M}+1$ )<sup>+</sup>

#### Preparation 60

#### 6-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)phenyl]-4-oxo-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-3-carbaldehyde

**[0149]** Tetrapropylammonium perruthenate (5mg, 0.014mmol) was added to a suspension of the title compound of preparation 59 (130mg, 0.26mmol), 4Å molecular sieves (150mg) and N-methylmorpholine N-oxide (50mg, 0.4mmol) in dichloromethane (5ml) and acetonitrile (2ml), and the reaction was stirred at room temperature for 2 hours under a nitrogen atmosphere. The reaction mixture was purified directly by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol (99:1 to 94:6), to afford the title compound, (70mg).

$\delta$  ( $\text{CDCl}_3$ ) : 0.99 (3H, t), 1.66 (3H, t), 2.00 (2H, m), 2.25 (3H, s), 2.48 (4H, m), 3.10 (4H, m), 4.40 (2H, q), 4.73 (2H, t), 7.18 (1H, d), 7.88 (1H, d), 8.98 (1H, s), 10.46 (1H, s), 10.98 (1H, s).

LRMS : m/z 489 ( $\text{M}+1$ )<sup>+</sup>

#### Preparation 61

#### 1-Cyclopentyl-5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)-phenyl]carbonylamino-3-ethyl-1H-pyrazole-4-carboxamide

**[0150]** N-Ethyl-diisopropylamine (410mg, 3.16mmol) was added to a suspension of the title compound of preparation 53 (400mg, 1.05mmol) and 5-amino-1-cyclopentyl-3-ethyl-4-pyrazolecarboxamide (WO 9628448) (210mg, 0.95mmol) and 2-chloro-1-methyl pyridinium chloride (403mg, 1.58mmol) in dichloromethane (5ml), and the reaction was stirred at room temperature for 72 hours. The reaction mixture was diluted with dichloromethane (30ml), washed consecutively with water (10ml), saturated sodium bicarbonate solution (10ml), and brine (10ml), dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol:0.88 ammonia (90:10:0 to 90:10:1) and repeated using dichloromethane:methanol:0.88 ammonia (100:0:1 to 94:4:1) to afford the title compound, (263mg).

$\delta$  ( $\text{CDCl}_3$ ) : 1.04 (3H, t), 1.33 (3H, t), 1.58 (3H, t), 1.65 (2H, m), 1.94 (2H, m), 2.10 (4H, m), 2.41 (2H, q), 2.54 (4H, m), 2.81 (2H, q), 3.10 (4H, m), 4.52 (1H, m), 4.79 (2H, q), 5.58 (2H, s), 8.69 (1H, s), 8.82 (1H, s), 10.45 (1H, s). LRMS : m/z 548 ( $\text{M}+1$ )<sup>+</sup>

#### Synthesis of the Compounds of Formulae IA and IB

#### Reference Example 1

#### 6-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-1-n-propyl-3-(pyridin-2-yl)methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0151]** A mixture of the title compound of preparation 37 (32mg, 0.08mmol), chlorosulphonic acid (140mg, 1.2mmol) and thionyl chloride (48mg, 0.40mmol) in dichloromethane (0.5ml) was stirred at room temperature for 18 hours. Ice (2g) was added, followed by a solution of N-ethylpiperazine (570mg, 5mmol) in dichloromethane (20ml) and the reaction stirred for a further hour. The mixture was poured into water (20ml), the layers separated and the aqueous phase extracted with dichloromethane (3x20ml). The combined organic solutions were dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol (100:0 to 95:5) to afford the title compound, (42mg).

$\delta$  ( $\text{CDCl}_3$ ) : 0.84 (3H, t), 0.98 (3H, t), 1.16 (3H, t), 1.83 (2H, m), 2.00 (2H, m), 2.36 (2H, q), 2.48 (4H, m), 3.02 (4H, m), 4.20 (2H, t), 4.26 (2H, t), 4.63 (2H, s), 7.12 (2H, m), 7.38 (1H, d), 7.57 (1H, m), 7.80 (1H, d), 8.45 (1H, d), 8.93 (1H, s), 10.60 (1H, s).

LRMS : m/z 580 ( $\text{M}+1$ )<sup>+</sup>

## Reference Example 2

6-[5-(4-Methylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-1-n-propyl-3-(pyrimidin-2-yl)methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0152]** Obtained as a white solid (38 %) from the title compound of preparation 38 and N-methylpiperazine, using a similar procedure to that described in example 1, except purification was achieved by ether trituration.

Found : C, 54.14; H, 5.83; N, 18.61.  $C_{27}H_{34}N_8O_4S \cdot 0.5CH_2Cl_2$  requires C, 54.22; H, 5.79; N, 18.39%.

$\delta$  ( $CDCl_3$ ) : 0.84 (3H, t), 1.14 (3H, t), 1.86 (2H, m), 1.99 (2H, m), 2.22 (3H, s), 2.45 (4H, m), 3.04 (4H, m), 4.15 (2H, t), 4.20 (2H, t), 4.84 (2H, s), 7.12 (2H, m), 7.80 (1H, d), 8.62 (2H, d), 8.96 (1H, s), 10.55 (1H, s).

LRMS : m/z 567 (M+1)<sup>+</sup>

## Reference Example 3

6-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-1-n-propyl-3-(pyrimidin-2-yl)methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0153]** Obtained as a pale pink solid (45%) from the title compound of preparation 38 and N-ethylpiperazine, using a similar procedure to that described in example 1, except purification was achieved by diethyl ether trituration.

Found : C, 55.26; H, 6.37; N, 18.46.  $C_{28}H_{36}N_8O_4S \cdot 1.5H_2O$  requires C, 55.34; H, 6.47; N, 18.44%.

$\delta$  ( $CDCl_3$ ) : 0.84 (3H, t), 0.99 (3H, t), 1.14 (3H, t), 1.86 (2H, m), 1.98 (2H, m), 2.38 (2H, q), 2.48 (4H, m), 3.03 (4H, m), 4.14 (2H, t), 4.20 (2H, t), 4.84 (2H, s), 7.12 (2H, m), 7.81 (1H, d), 8.63 (2H, d), 8.94 (1H, s), 10.54 (1H, s).

LRMS : m/z 581 (M+1)<sup>+</sup>

## Reference Example 4

3-Benzyl-6-[2-ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)phenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0154]** Powdered potassium hydroxide (78mg, 1.38mmol) was added to a suspension of the title compound of preparation 42 (254mg, 0.46mmol) in 3-methyl-3-pentanol (5ml), and the reaction heated at 110°C for 18 hours. The cooled reaction mixture was partitioned between ethyl acetate (10ml) and water (10ml), the phases separated, and the aqueous layer extracted with further ethyl acetate (2x10ml). The combined organic solutions were dried ( $Na_2SO_4$ ), and evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol:0.88 ammonia (100:0:0 to 85:15:1) to afford the title compound as a white foam, (23mg).

Found : C, 60.44; H, 6.15; N, 14.92.  $C_{28}H_{34}N_6O_4S$  requires C, 61.05; H, 6.18; N, 15.26%.

$\delta$  ( $CDCl_3$ ) : 0.94 (3H, t), 1.65 (3H, t), 1.97 (2H, m), 2.26 (3H, s), 2.48 (4H, m), 3.08 (4H, m), 4.35 (6H, m), 7.18 (2H, m), 7.26 (2H, m), 7.47 (2H, m), 7.86 (1H, d), 8.82 (1H, s), 10.70 (1H, s).

LRMS : m/z 551 (M+1)<sup>+</sup>

## Reference Example 5

3-Benzyl-6-[2-ethoxy-5-[4-(2-hydroxyethyl)piperazin-1-ylsulphonyl]phenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0155]** A mixture of the title compound of preparation 43 (477mg, 0.80mmol) and potassium t-butoxide (313mg, 2.79mmol) in isopropanol (25ml), was heated under reflux for 18 hours, then cooled. Water (50ml) was added, the mixture neutralised with 2N hydrochloric acid and concentrated under reduced pressure. This solution was partitioned between ethyl acetate (50ml) and sodium bicarbonate solution (25ml), the layers separated and the aqueous phase extracted with ethyl acetate (2x25ml). The combined organic solutions were dried ( $Na_2SO_4$ ) and evaporated under reduced pressure. The residual brown oil was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol (100:0 to 95:5), and trituted with ether to afford the title compound, (112mg).

Found : C, 59.63; H, 6.22; N, 14.34.  $C_{29}H_{36}N_6O_5S$  requires C, 59.98; H, 6.20; N, 14.49%.

$\delta$  ( $CDCl_3$ ) : 0.95 (3H, t), 1.63 (3H, t), 1.96 (2H, m), 2.26 (1H, s), 2.55 (2H, t), 2.60 (4H, m), 3.09 (4H, m), 3.58 (2H, m), 4.35 (6H, m), 7.18 (2H, d), 7.26 (2H, m), 7.46 (2H, m), 7.87 (1H, d), 8.83 (1H, s), 10.70 (1H, s).

LRMS : m/z 581 (M+1)<sup>+</sup>

Reference Example 66-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)phenyl]-1-ethyl-3-phenyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0156]** A mixture of the title compound of preparation 44 (180mg, 0.34mmol) and potassium t-butoxide (116mg, 1.0mmol) in ethanol (10ml) was heated under reflux for 4 hours. The cooled reaction mixture was evaporated under reduced pressure and the residue purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol (100:0 to 95:5) to afford the title compound, (110mg).

Found : C, 58.74; H, 5.88; N, 15.66.  $C_{26}H_{30}N_6O_4S$  requires C, 58.74; H, 5.88; N, 15.81%.

$\delta$  ( $CDCl_3$ ) : 1.58 (3H, t), 1.69 (3H, t), 2.27 (3H, s), 2.52 (4H, m), 3.14 (4H, m), 4.40 (2H, q), 4.51 (4H, q), 7.19 (1H, d), 7.39 (1H, m), 7.45 (1H, m), 7.90 (1H, d), 8.42 (1H, d), 8.90 (1H, s), 10.88 (1H, s). LRMS m/z 523 (M+1)<sup>+</sup>

Reference Example 71-Ethyl-6-[5-(4-methylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-3-phenyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0157]** A suspension of sodium (25mg, 1.1mmol) in n-propanol (1ml) was added to the title compound of example 6 (80mg, 0.15mmol) in n-propanol (1ml), and the reaction mixture heated under reflux for 72 hours. Further sodium (100mg, 4.34mmol) and n-propanol (5ml) were added portionwise over a further 48 hours, then the mixture cooled and evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel, using dichloromethane:methanol:0.88 ammonia (95:5:0.5) as eluant, to afford the title compound, (8mg).

$\delta$  ( $CDCl_3$ ) : 1.19 (3H, t), 1.58 (3H, t), 2.02 (2H, m), 2.28 (3H, s), 2.52 (4H, m), 3.13 (4H, m), 4.24 (2H, t), 4.48 (2H, q), 7.18 (1H, d), 7.37 (1H, m), 7.43 (2H, m), 7.86 (1H, d), 8.40 (2H, d), 8.86 (1H, s), 10.90 (1H, s).

LRMS : m/z 536 (M+1)<sup>+</sup>

Reference Example 83-(Benzyloxy)methyl-6-[2-isopropoxy-5-(4-methylpiperazin-1-ylsulphonyl)phenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one andReference Example 93-(Benzyloxy)methyl-6-[2-ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)phenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0158]** A mixture of the title compound of preparation 45 (1.80g, 3.1mmol) and potassium t-butoxide (1.4g, 12.4mmol) in isopropanol (40ml) was heated under reflux for 10 hours and stirred for a further 16 hours at room temperature. Water (5ml) was added, the mixture acidified to pH 6 with 2N hydrochloric acid, and concentrated under reduced pressure to remove the isopropanol and the resulting precipitate filtered and dried. This solid was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol (99:1 to 92:8) and repeated using an elution gradient of dichloromethane:isopropanol:0.88 ammonia (98:2:0.1 to 90:10:0.5) to afford, after trituration with ethyl acetate, the title compound of example 8, (15mg).

$\delta$  ( $CDCl_3$ ) : 0.96 (3H, t), 1.59 (6H, d), 2.03 (2H, m), 2.48 (3H, s), 2.50 (4H, m), 3.10 (4H, m), 4.30 (2H, t), 4.62 (2H, s), 4.92 (1H, m), 5.05 (2H, s), 7.17 (1H, d), 7.34 (5H, m), 7.84 (1H, d), 9.00 (1H, s), 10.76 (1H, s).

LRMS : m/z 595 (M+1)<sup>+</sup> and the title compound of example 9, (320mg).

Found : C, 59.78; H, 6.21; N, 14.37.  $C_{29}H_{36}N_6O_5S$  requires C, 59.98; H, 6.25; N, 14.47%.

$\delta$  ( $CDCl_3$ ) : 0.97 (3H, t), 1.64 (3H, t), 2.02 (2H, m), 2.26 (3H, s), 2.48 (4H, m), 3.10 (4H, m), 4.30 (2H, t), 4.39 (2H, q), 4.61 (2H, s), 5.05 (2H, s), 7.17 (1H, d), 7.34 (5H, m), 7.82 (1H, d), 8.98 (1H, s), 10.64 (1H, s).

LRMS : m/z 581 (M+1)<sup>+</sup>

Reference Example 106-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)phenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0159]** Obtained as an off-white solid (43%) from the title compound of preparation 46, using a similar procedure to

that described in example 5, except the title compound was isolated by trituration with diethyl ether.

$\delta$  (CDCl<sub>3</sub>) : 0.95 (3H, t), 1.64 (3H, t), 1.97 (2H, m), 2.27 (3H, s), 2.50 (4H, m), 2.62 (3H, s), 3.12 (4H, m), 4.30 (2H, t), 4.40 (2H, q), 7.19 (1H, d), 7.89 (1H, d), 8.82 (1H, s), 10.68 (1H, s).

LRMS : m/z 475 (M+1)<sup>+</sup>

#### Reference Example 11

6-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)phenyl]-3-isopropyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0160]** A solution of the title compound of preparation 40 (730mg, 1.4mmol) in dichloromethane (3ml) was added dropwise to solution of the title compound of preparation 20 (243mg, 1.2mmol) in pyridine (10ml), and the reaction stirred at room temperature for 5 days. The reaction mixture was concentrated under reduced pressure and azeotroped with toluene. The residual orange solid was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol (99:1 to 90:10), the product suspended in dichloromethane and the suspension filtered. The filtrate was concentrated under reduced pressure and the residue partitioned between ethyl acetate (25ml) and water (10ml), the phases separated, the organic layer washed with brine (10ml), dried (MgSO<sub>4</sub>) and evaporated under reduced pressure, to afford the title compound as a cream foam, (48mg).

$\delta$  (CDCl<sub>3</sub>) : 0.90 (3H, t), 1.38 (6H, d), 1.62 (3H, t), 1.89 (2H, m), 2.26 (3H, s), 2.48 (4H, m), 3.05 (4H, m), 3.26 (1H, m), 4.00 (2H, t), 4.42 (2H, q), 7.18 (1H, d), 7.92 (1H, d), 8.62 (1H, s), 10.22 (1H, s). LRMS : m/z 521 (M+18)<sup>+</sup>

#### Reference Example 12

3-(Cyclopropyl)methyl-6-[2-ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)phenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0161]** The title compound of preparation 40 (490mg, 1.4mmol) was added to a solution of the title compound of preparation 21 (250mg, 1.13mmol) in pyridine (6ml) and the reaction stirred at room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure, azeotroped with toluene and the residue partitioned between dichloromethane (40ml) and sodium bicarbonate solution (20ml). The phases were separated, the organic layer washed with brine (20ml), dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to give a yellow oil.

**[0162]** A mixture of this intermediate carboxamide, and potassium t-butoxide (380mg, 3.38mmol) in isopropanol (5ml) was heated under reflux for 18 hours, then cooled. The reaction mixture was concentrated under reduced pressure, the residue partitioned between ethyl acetate (15ml) and water (15ml) and the layers separated. The aqueous layer was neutralised with 2N hydrochloric acid, extracted with ethyl acetate (3x15ml), and these combined organic extracts washed with brine (20ml), dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel twice, using an elution gradient of dichloromethane:isopropanol (99:1 to 90:10) to afford the title compound, (60mg).

$\delta$  (CDCl<sub>3</sub>) : 0.34 (2H, m), 0.46 (2H, m), 0.95 (3H, t), 1.30 (1H, m), 1.65 (3H, t), 1.98 (2H, m), 2.28 (3H, s), 2.51 (4H, m), 2.90 (2H, d), 3.10 (4H, m), 4.38 (4H, m), 7.18 (1H, d), 7.86 (1H, d), 8.83 (1H, s), 10.70 (1H, s).

LRMS : m/z 515 (M+1)<sup>+</sup>

#### Reference Example 13

6-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)phenyl]-3-(morpholinomethyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0163]** A mixture of the title compound of preparation 60 (70mg, 0.14mmol), morpholine (15ml, 0.17mmol), sodium triacetoxyborohydride (43mg, 0.20mmol) and acetic acid (10ml, 0.17mmol) in dichloromethane (2ml) was stirred at room temperature for 18 hours. The reaction mixture was partitioned between dichloromethane (10ml) and dilute sodium bicarbonate solution (10ml), the phases separated and the aqueous layer extracted with dichloromethane (2x10ml). The combined organic solutions were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol (99:1 to 94:6) and recrystallised from ethyl acetate, to afford the title compound, (30mg).

$\delta$  (CDCl<sub>3</sub>) : 1.00 (3H, t), 1.63 (3H, t), 2.05 (2H, m), 2.26 (3H, s), 2.48 (4H, m), 2.58 (4H, t), 3.09 (4H, m), 3.67 (4H, t), 4.00 (2H, s), 4.36 (4H, m), 7.16 (1H, d), 7.84 (1H, d), 9.00 (1H, s), 10.62 (1H, s).

LRMS : m/z 560 (M+1)<sup>+</sup>

## Reference Example 14

3-Methyl-6-[5-(4-methylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-1-(pyridin-2-yl)methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0164]** A mixture of the title compound of preparation 28 (85mg, 0.23mmol) in chlorosulphonic acid (264mg, 2.3mmol) and thionyl chloride (81mg, 0.68mmol) was stirred at room temperature for 18 hours. The mixture was cooled in an ice-bath, ice (1g) added, followed by ethanol (5ml) and N-methylpiperazine (340mg, 3.4mmol), and the reaction stirred for 15 minutes at room temperature. The mixture was evaporated under reduced pressure and the residue purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol (98:2 to 92:8) to afford the title compound, (89mg).

Found : C, 57.13; H, 5.81; N, 17.79.  $C_{26}H_{31}N_7O_4S \cdot 0.5H_2O$  requires C, 57.13; H, 5.90; N, 17.94%.

$\delta$  ( $CDCl_3$ ) : 1.17 (3H, t), 2.02 (2H, m), 2.21 (3H, s), 2.42 (4H, m), 2.60 (3H, s), 3.02 (4H, m), 4.23 (2H, t), 5.62 (2H, s), 7.03 (1H, d), 7.16 (2H, m), 7.60 (1H, m), 7.82 (1H, d), 8.57 (1H, d), 8.75 (1H, s), 10.73 (1H, s).

LRMS : m/z 538 (M+1)<sup>+</sup>

## Reference Example 15

1-Cyclopentyl-3-ethyl-6-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0165]** 1-Cyclopentyl-3-ethyl-6-(2-n-propoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (WO 96/28448) (500mg, 1.36mmol) was added portionwise to chlorosulphonic acid (1.6g, 13.6mmol) and the reaction stirred at room temperature for 18 hours. The reaction was poured into a mixture of ice water (30ml) and dichloromethane (30ml) with stirring, the layers separated and the aqueous extracted with dichloromethane (2x30ml). The combined organic solutions were washed with brine (30ml), dried ( $Na_2SO_4$ ) and evaporated under reduced pressure, to give a foam. N-Ethylpiperazine (108mg, 0.95mmol) was added dropwise to an ice-cold solution of this intermediate sulphonyl chloride in dichloromethane (3ml) and the reaction stirred at room temperature for 2 hours. The mixture was diluted with dichloromethane (10ml), washed consecutively with water (5ml), saturated sodium bicarbonate solution (5ml) and brine (5ml), dried ( $Na_2SO_4$ ) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol (100:0 to 96:4) to afford the title compound, (81mg).

Found : C, 59.30; H, 7.06; N, 15.48.  $C_{27}H_{38}N_6O_4S$  requires C, 59.75; H, 7.06; N, 15.48%.

$\delta$  ( $CDCl_3$ ) : 1.02 (3H, t), 1.19 (3H, t), 1.38 (3H, t), 1.75 (2H, m), 2.02 (4H, m), 2.16 (4H, m), 2.40 (2H, q), 2.54 (4H, m), 2.98 (2H, q), 3.10 (4H, m), 5.25 (2H, t), 5.18 (1H, m), 7.18 (1H, d), 7.86 (1H, d), 8.84 (1H, s), 10.70 (1H, s).

LRMS : m/z 543 (M+1)<sup>+</sup>

## Reference Example 16

3-Methyl-6-[5-(4-methylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-2-(pyridin-2-yl)methyl-2,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0166]** Obtained (19%) from the title compound of preparation 29, using the procedure of example 14.

$\delta$  ( $CDCl_3$ ) : 1.14 (3H, t), 2.00 (2H, m), 2.22 (3H, s), 2.44 (4H, m), 2.72 (3H, s), 3.02 (4H, m), 4.22 (2H, t), 5.54 (2H, s), 7.11 (1H, d), 7.20 (2H, m), 7.62 (1H, m), 7.82 (1H, d), 8.55 (1H, d), 8.94 (1H, s), 10.52 (1H, s).

LRMS : m/z 538 (M+1)<sup>+</sup>

## Reference Example 17

3-Methyl-6-[5-(4-methylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-2-(pyrimidin-2-yl)-2,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0167]** Obtained (59%) from the title compound of preparation 30, using the procedure of example 14.

Found : C, 53.65; H, 5.48; N, 20.63.  $C_{24}H_{28}N_8O_4S \cdot 0.8H_2O$  requires C, 53.48; H, 5.54; N, 20.79%.

$\delta$  ( $CDCl_3$ ) : 1.22 (3H, t), 2.06 (2H, m), 2.27 (3H, s), 2.50 (4H, m), 3.10 (4H, m), 3.19 (3H, s), 4.30 (2H, t), 7.18 (1H, d), 7.38 (1H, m), 7.88 (1H, d), 8.90 (2H, d), 9.05 (1H, s).

LRMS : m/z 525 (M+1)<sup>+</sup>

Example 18

6-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-1-ethyl-3-(pyrazin-2-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0168]** Potassium t-butoxide (103mg, 0.9mmol) was added to a suspension of the title compound of preparation 55 (170mg, 0.3mmol) in ethanol (5ml) and the reaction stirred at 100°C in a sealed vessel for 5 hours. The cooled reaction mixture was evaporated under reduced pressure and the residue purified by column chromatography on silica gel, using dichloromethane:methanol (85:15) as eluant, to afford the title compound as a brown solid, (130mg).

Found : C, 51.32; H, 5.31; N, 21.90. C<sub>24</sub>H<sub>29</sub>N<sub>9</sub>O<sub>4</sub>S; 1.4H<sub>2</sub>O requires C, 51.04; H, 5.67; N, 22.32%.

δ (CDCl<sub>3</sub>) : 1.04 (3H, t), 1.62 (6H, m), 2.42 (2H, q), 2.59 (4H, m), 3.18 (4H, m), 4.61 (2H, q), 4.80 (2H, q), 8.61 (1H, s), 8.75 (2H, m), 9.13 (1H, s), 10.00 (1H, s), 10.92 (1H, s).

LRMS : m/z 540 (M + 1)<sup>+</sup>

Example 19

6-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-1-n-propyl-3-(pyrazin-2-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0169]** Obtained (45%) from the title compound of preparation 56, using a similar procedure to that described in example 18, but using ethyl acetate:methanol (90:10) as chromatographic eluant.

δ (CDCl<sub>3</sub>) : 1.01 (6H, m), 1.62 (3H, t), 2.08 (2H, m), 2.43 (2H, q), 2.58 (4H, m), 3.17 (4H, m), 4.55 (2H, t), 4.81 (2H, q), 8.61 (1H, s), 8.75 (2H, m), 9.14 (1H, s), 9.99 (1H, s), 10.90 (1H, s).

LRMS : m/z 554 (M + 1)<sup>+</sup>

Example 20

1-Ethyl-6-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(isopropoxy)pyridin-3-yl]-3-(pyrazin-2-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0170]** A mixture of the title compound of example 18 (80mg, 0.15mmol) and potassium t-butoxide (50mg, 0.44mmol) in isopropanol (4ml) was heated under reflux for 48 hours. The cooled reaction mixture was evaporated under reduced pressure and the residual brown solid purified by column chromatography on silica gel, using ethyl acetate:methanol (90:10) as eluant, to afford the title compound, (30mg).

Found : C, 53.22; H, 5.77; N, 21.60.

C<sub>25</sub>H<sub>31</sub>N<sub>9</sub>O<sub>4</sub>S; 0.5H<sub>2</sub>O; 0.2C<sub>2</sub>H<sub>5</sub>O<sub>2</sub>CH<sub>3</sub> requires C, 53.40; H, 5.84; N, 21.72%.

δ (CDCl<sub>3</sub>) : 1.04 (3H, t), 1.60 (9H, m), 2.43 (2H, q), 2.59 (4H, m), 3.18 (4H, m), 4.60 (2H, q), 5.76 (1H, m), 8.61 (1H, s), 8.74 (2H, m), 9.14 (1H, s), 9.99 (1H, s), 11.01 (1H, s).

LRMS : m/z 554 (M+1)<sup>+</sup>

Example 21

6-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-1-ethyl-3-phenyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0171]** Obtained (38 %) from the title compound of preparation 57, using a similar procedure to that described in example 18, but using ethyl acetate:methanol (95:5) as chromatographic eluant.

δ (CDCl<sub>3</sub>) : 1.01 (3H, t), 1.56 (6H, m), 2.40 (2H, q), 2.56 (4H, m), 3.13 (4H, m), 4.46 (2H, q), 4.76 (2H, q), 7.38 (1H, m), 7.43 (2H, m), 8.39 (2H, d), 8.66 (1H, s), 9.07 (1H, s), 10.78 (1H, s).

LRMS : m/z 539 (M+2)<sup>+</sup>

Example 22

1-Ethyl-6-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-3-phenyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0172]** A mixture of potassium bis(trimethylsilyl)amide (359mg, 1.8mmol) in 2-methoxyethanol (20ml) was heated at 90°C for 30 minutes, then cooled to room temperature. The title compound of example 21 (200mg, 0.36mmol) was

added and the reaction heated under reflux for 18 hours and allowed to cool. The mixture was concentrated under reduced pressure, the residue partitioned between ethyl acetate (20ml) and water (20ml) and the phases separated. The aqueous layer was extracted with ethyl acetate (2x20ml), the combined organic solutions dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using dichloromethane:methanol (97:3) as eluant, to afford the title compound, (105mg).

Found : C, 56.83; H, 5.88; N, 16.99. C<sub>27</sub>H<sub>33</sub>N<sub>7</sub>O<sub>5</sub>S requires C, 57.13; H, 5.86; N, 17.27%.

δ (CDCl<sub>3</sub>) : 1.04 (3H, t), 1.59 (3H, t), 2.42 (2H, q), 2.58 (4H, m), 3.17 (4H, m), 3.59 (3H, s), 3.88 (2H, t), 4.51 (2H, q), 4.81 (2H, t), 7.39 (1H, m), 7.45 (2H, m), 8.40 (2H, m), 8.70 (1H, s), 9.04 (1H, s), 10.92 (1H, s).

LRMS : m/z 568 (M + 1)<sup>+</sup>

#### Example 23

#### 3-(Benzyloxy)methyl-6-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-1-ethyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0173]** A mixture of the title compound of preparation 58 (940mg, 1.57mmol) and sodium ethoxide (272mg, 4.0mmol) in ethanol (25ml) was heated under reflux for 8 hours. The cooled reaction mixture was diluted with water (25ml), and the mixture extracted with dichloromethane (3x50ml). The combined organic extracts were dried (MgSO<sub>4</sub>) and evaporated under reduced pressure, to afford the title compound, (767mg).

δ (CDCl<sub>3</sub>) : 1.00 (3H, t), 1.55 (6H, m), 2.39 (2H, q), 2.52 (4H, m), 3.12 (4H, m), 4.40 (2H, q), 4.75 (4H, m), 4.85 (2H, s), 7.30 (3H, m), 7.40 (2H, m), 8.64 (1H, s), 9.04 (1H, s), 10.69 (1H, s).

LRMS : m/z 582 (M + 1)<sup>+</sup>

#### Example 24

#### 6-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-1-ethyl-3-hydroxymethyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0174]** Formic acid (1.5ml) was added to a mixture of the title compound of example 23 (750mg, 1.3mmol) and 10% palladium on charcoal (750mg) in ethyl acetate (15ml), and the reaction stirred under a nitrogen atmosphere at room temperature for 24 hours. The reaction mixture was filtered through Arbocel, the filter pad washed with water (30ml) and ethyl acetate (30ml), and the filtrate basified using 2N sodium hydroxide solution. The layers were separated, the aqueous extracted with dichloromethane (3x100ml), and the combined organic solutions dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was triturated with ether, to afford the title compound as a white solid, (375mg).

δ (CDCl<sub>3</sub>) : 1.02 (3H, t), 1.54 (3H, t), 1.60 (3H, t), 2.42 (2H, q), 2.57 (4H, m), 3.16 (4H, m), 4.42 (2H, q), 4.60 (1H, t), 4.79 (2H, q), 4.92 (2H, d), 8.70 (1H, s), 9.08 (1H, s), 10.88 (1H, s).

LRMS : m/z 492 (M + 1)<sup>+</sup>

#### Example 25

#### 1-Cyclopentyl-6-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

**[0175]** A mixture of the title compound of preparation 61 (253mg, 0.46mmol) and potassium bis(trimethylsilyl)amide (110mg, 0.55mmol) in ethanol (10ml) was heated in a sealed vessel at 110°C, for 18 hours, then cooled. The reaction mixture was concentrated under reduced pressure, the residue dissolved in dichloromethane (30ml), the solution washed with water (20ml), and the pH of the mixture adjusted to 8 using hydrochloric acid. The layers were separated, the organic washed with brine (10ml), dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel, using an elution gradient of dichloromethane saturated with 0.88 ammonia:methanol (100:0 to 96.4:0.4), to afford the title compound as a white foam, (210mg).

Found : C, 56.51; H, 6.71; N, 18.16. C<sub>25</sub>H<sub>35</sub>N<sub>7</sub>O<sub>4</sub>S requires C, 56.69; H, 6.66; N, 18.51%.

δ (CDCl<sub>3</sub>) : 1.03 (3H, t), 1.38 (3H, t), 1.59 (3H, t), 1.75 (2H, m), 2.00 (2H, m), 2.16 (4H, m), 2.42 (2H, q), 2.57 (4H, m), 2.99 (2H, q), 3.15 (4H, m), 4.77 (2H, q), 5.19 (1H, m), 8.68 (1H, s), 9.07 (1H, s), 10.62 (1H, s).

LRMS : m/z 530 (M + 1)<sup>+</sup>

## Biological Activity

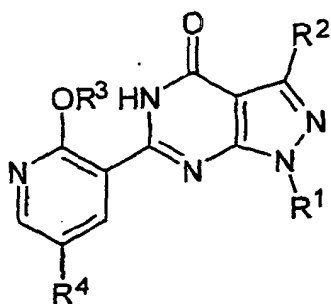
[0176] Compounds of the invention were found to have *in vitro* activities as inhibitors of cGMP PDE5 with IC<sub>50</sub> values of less than about 100 nM.

[0177] The following Table illustrates the *in vitro* activities for a range of compounds of the invention as inhibitors of cGMP PDE5.

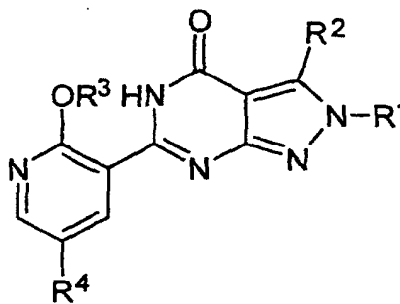
Example	TC <sub>50</sub> (nM)
18	8.10
19	7.67
21	4.60

## Claims

1. A compound of formula IA, or of formula IB:



IA



IB

wherein

R¹ represents linear or cyclic C<sub>2-5</sub> alkyl, Het or C<sub>1-3</sub> alkylHet, in which both latter cases, Het represents a six-membered aromatic ring containing one or two nitrogen atoms;

R² represents linear or branched, cyclic, acyclic or part-cyclic C<sub>1-4</sub> alkyl (which alkyl group is optionally terminated by OH), C<sub>1-3</sub> alkylHet (in which Het represents a six-membered heterocyclic group containing one or two nitrogen atoms), C<sub>1-3</sub> alkylaryl (the alkyl group of which is optionally interrupted by an O atom), aryl or Het (in which Het represents a six-membered heterocyclic group containing one or two nitrogen atoms);

R³ represents linear or branched C<sub>1-6</sub> alkyl, optionally terminated by OH or O-methyl;

R⁴ represents SO<sub>2</sub>NR<sup>12</sup>R<sup>13</sup>;

R<sup>12</sup> and R<sup>13</sup>, together with the nitrogen atom to which they are attached, represent 4-R<sup>14</sup>-piperazinyl, in which R<sup>14</sup> represents C<sub>1-6</sub> alkyl, optionally terminated by OH; and

R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10a</sup>, R<sup>10b</sup>, R<sup>11a</sup> and R<sup>11b</sup> independently represent H or C<sub>1-6</sub> alkyl; and

the term "aryl" means a six- to ten-membered carbocyclic aromatic group, which group is optionally substituted with one or more substituents selected from aryl, C<sub>1-6</sub> alkyl, Het, halo, cyano, nitro, OR<sup>5</sup>, C(O)R<sup>6</sup>, C(O)OR<sup>7</sup>, C(O)NR<sup>8</sup>R<sup>9</sup>, NR<sup>10a</sup>R<sup>10b</sup>, SO<sub>2</sub>NR<sup>11a</sup>R<sup>11b</sup> and N(H)SO<sub>2</sub>R<sup>11a</sup>;

or a pharmaceutically, or a veterinarily, acceptable salt or solvate thereof.

2. A compound as claimed in Claim 1, wherein R³ represents linear or branched C<sub>1-4</sub> alkyl, optionally terminated by OH or O-methyl.

3. A compound as claimed in Claim 1 or Claim 2, wherein R¹ represents ethyl, *n*-propyl or cyclopentyl, pyrimidin-2-yl or -CH<sub>2</sub>-(pyridin-2-yl).

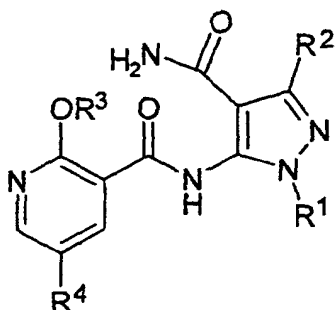
4. A compound as claimed in any one of the preceding claims, wherein R² represents methyl, hydroxymethyl, ethyl,



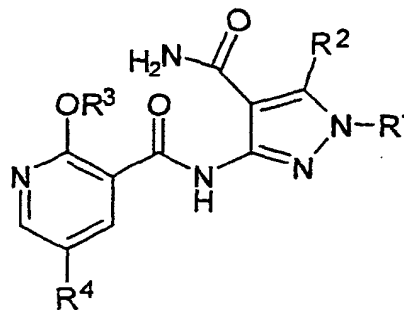
propyl or cyclopropylmethyl,  $-\text{CH}_2\text{-(pyridin-2-yl)}$ ,  $-\text{CH}_2\text{-(pyrimidin-2-yl)}$ ,  $-\text{CH}_2\text{-(morpholinyl)}$ ,  $-\text{CH}_2\text{-(pyrazin-2-yl)}$ , benzyl,  $-\text{CH}_2\text{OCH}_2\text{-phenyl}$ , phenyl or pyrazin-2-yl.

5. A compound as claimed in any one of the preceding claims, wherein  $\text{R}^3$  represents linear or branched  $\text{C}_{2-3}$  alkyl, optionally terminated by  $\text{OCH}_3$ .
6. A compound as claimed in any one of the preceding claims, wherein  $\text{R}^{12}$  and  $\text{R}^{13}$ , together with the nitrogen atom to which they are attached, represent 4- $\text{R}^{14}$ -piperazinyl, in which  $\text{R}^{14}$  represents  $\text{C}_{1-3}$  alkyl optionally terminated by OH.
7. A compound as defined in any one of Claims 1 to 6 for use as a pharmaceutical.
8. A compound as defined in any one of Claims 1 to 6 for use as an animal medicament.
9. A formulation comprising a compound as defined in any one of Claims 1 to 6 in admixture with a pharmaceutically or veterinarily acceptable adjuvant, diluent or carrier.
10. A formulation as claimed in Claim 9, which is a pharmaceutical formulation.
11. A formulation as claimed in Claim 9, which is a veterinary formulation.
12. The use of a compound as defined in any one of Claims 1 to 6 in the manufacture of a medicament for the curative or prophylactic treatment of a medical condition for which inhibition of cGMP PDE5 is desired.
13. Use as claimed in Claim 12, wherein the condition is male erectile dysfunction, female sexual dysfunction, premature labour, dysmenorrhoea, benign prostatic hyperplasia (BPH), bladder outlet obstruction, incontinence, stable or unstable variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma, a disease **characterised by** disorders of gut motility, pre-eclampsia, Kawasaki's syndrome, nitrate tolerance, multiple sclerosis, peripheral diabetic neuropathy, stroke, Alzheimer's disease, acute respiratory failure, psoriasis, skin necrosis, cancer metastasis or baldness.
14. A process for the preparation of a compound of formula IA, or of formula IB, as defined in Claim 1, which comprises:

(a) cyclisation of a corresponding compound of formula IIA, or of formula IIB, respectively:



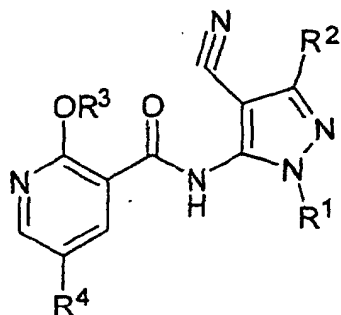
IIA



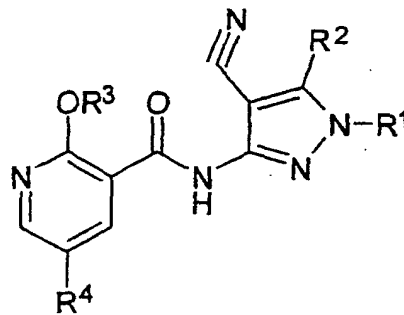
IIB

wherein  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^4$  are as defined in Claim 1;

(b) cyclisation of a corresponding compound of formula VA, or of formula VB, respectively:



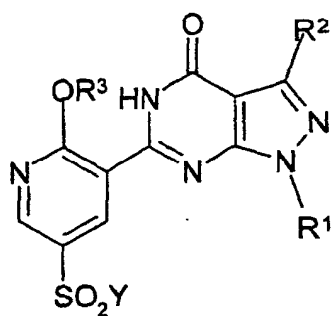
VA



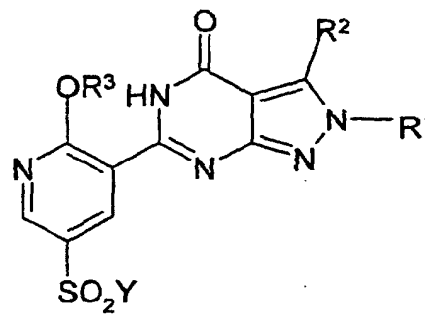
VB

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as defined in Claim 1;

(c) reaction of a corresponding compound of formula VIIA, or of formula VIIB, respectively:

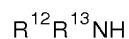


VIIA



VIIB

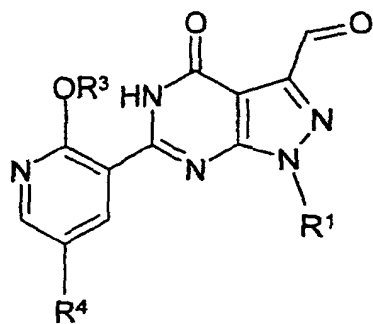
wherein Y is halo and R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined in Claim 1 with a compound of formula VIII:



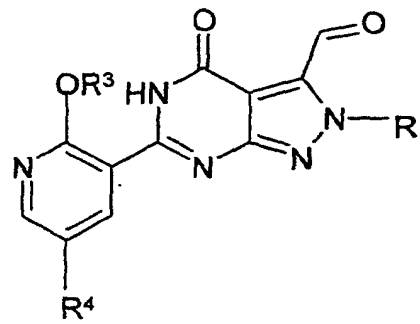
VIII

wherein R<sup>12</sup> and R<sup>13</sup> are as defined in Claim 1;

(d) for compounds of formulae IA and IB, in which R<sup>2</sup> represents C<sub>1-4</sub> alkyl, C<sub>1-3</sub> alkylHet or C<sub>1-3</sub> alkylaryl, reaction of a corresponding compound of formula XVIA, or of formula XVIB, respectively:

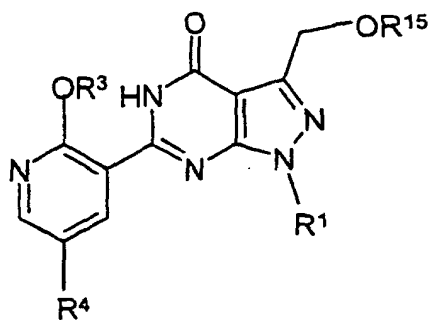


XVIA

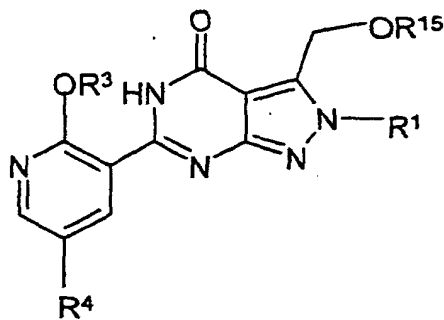


XVIB

wherein  $R^1$ ,  $R^3$  and  $R^4$  are as defined in Claim 1, with either an organometallic compound of formula  $R^{2a}M$ , in which M represents Li or MgHal, Hal represents halo and  $R^{2a}$  represents a group which provides the relevant group  $R^2$  upon reaction with the  $-C=O$  group which is attached to the pyrazole ring, followed by deoxygenation of the resultant secondary alcohol, or by reductive amination using a basic compound which provides an  $R^2$  group upon reaction with the  $-C=O$  group which is attached to the pyrazole ring;  
 (e) for compounds of formulae IA and IB in which  $R^2$  represents  $CH_2OH$ , deprotection of a corresponding compound of formula XVIIA, or of formula XVIIIB, respectively:



XVIIA



XVIIIB

wherein  $R^1$ ,  $R^3$  and  $R^4$  are as defined in Claim 1 and  $R^{15}$  represents an alcohol protecting group;  
 (f) for compounds of formula IA or IB in which  $R^1$  represents  $C_{2-5}$  alkyl, or  $C_{1-3}$  alkylHet, alkylation of a corresponding compound of formula IA, or of formula IB, respectively, in which  $R^1$  represents H;  
 (g) conversion, removal or introduction of a substituent on an aryl, or a Het, group in, or on the pyridinyl, or pyrazolo, unit of, a compound of formula IA or IB;  
 (h) conversion of one  $R^3$  group to another by alkoxide exchange;  
 (i) for compounds of formula IA or IB in which  $R^{12}$  and  $R^{13}$ , together with the nitrogen to which they are attached, form a 4- $R^{14}$ -piperazinyl group in which  $R^{14}$  represents  $C_{1-6}$  alkyl, alkylation of a corresponding compound of formula IA or IB in which  $R^{14}$  represents hydrogen; or  
 (j) deprotection of a protected derivative of a compound of formula IA or of formula IB.

15. A compound of formula IIA, or of formula IIB, as defined in Claim 14.

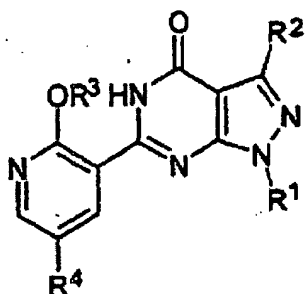
16. A compound of formula VA, or of formula VB, as defined in Claim 14.

17. A compound of formula VIIA, or of formula VIIB, as defined in Claim 14.

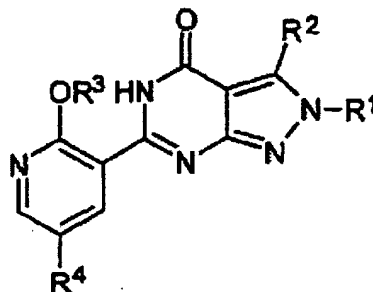
18. A compound of formula XVIIA, or of formula XVIIIB, as defined in Claim 14.

## Patentansprüche

1. Verbindung der Formel IA oder der Formel IB:



IA



IB

wobei

R<sup>1</sup> lineares oder cyclisches C<sub>2</sub>-C<sub>5</sub>-Alkyl, Het oder C<sub>1</sub>-C<sub>3</sub>-AlkylHet bedeutet, wobei in den beiden letzteren Fällen Het für einen sechsgliedrigen, aromatischen Ring steht, welcher ein oder zwei Stickstoffatome enthält;

R<sup>2</sup> bedeutet: lineares oder verzweigtes, cyclisches, acyclisches oder teilweise cyclisches C<sub>1</sub>-C<sub>4</sub>-Alkyl (wobei die Alkylgruppe optional mit OH endsubstituiert ist), C<sub>1</sub>-C<sub>3</sub>-AlkylHet (wobei Het für eine sechsgliedrige, heterocyclische Gruppe steht, welche ein oder zwei Stickstoffatome enthält),

C<sub>1</sub>-C<sub>3</sub>-Arylalkyl (dessen Alkylgruppe optional durch ein O-Atom unterbrochen ist), Aryl oder Het (wobei Het für eine sechsgliedrige, heterocyclische Gruppe steht, welche ein oder zwei Stickstoffatome enthält) ;

R<sup>3</sup> lineares oder verzweigtes C<sub>1</sub>-C<sub>6</sub>-Alkyl bedeutet, welches optional mit OH oder O-methyl endsubstituiert ist;

R<sup>4</sup> SO<sub>2</sub>NR<sup>12</sup>R<sup>13</sup> bedeutet;

R<sup>12</sup> und R<sup>13</sup> zusammen mit dem Stickstoffatom, an welches sie gebunden sind, 4-R<sup>14</sup>-Piperazinyl bedeuten, wobei R<sup>14</sup> C<sub>1</sub>-C<sub>6</sub>-Alkyl bedeutet, welches optional mit OH endsubstituiert ist; und

R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10a</sup>, R<sup>10b</sup>, R<sup>11a</sup> und R<sup>11b</sup> unabhängig voneinander für H oder C<sub>1</sub>-C<sub>6</sub>-Alkyl stehen; und

der Begriff "Aryl" eine sechs- bis zehngliedrige, carbocyclische, aromatische Gruppe bedeutet, welche optional mit einem oder mehr Substituenten ausgewählt aus Aryl, C<sub>1</sub>-C<sub>6</sub>-Alkyl, Het, Halogen, Cyano, Nitro, OR<sup>5</sup>, C(O)R<sup>6</sup>, C(O)OR<sup>7</sup>, C(O)NR<sup>8</sup>R<sup>9</sup>, NR<sup>10a</sup>R<sup>10b</sup>, SO<sub>2</sub>NR<sup>11a</sup>R<sup>11b</sup> und N(H)SO<sub>2</sub>R<sup>11a</sup> substituiert ist, oder ein pharmazeutisch oder veterinärmedizinisch akzeptables Salz oder Solvat davon.

2. Verbindung nach Anspruch 1, wobei R<sup>3</sup> für lineares oder verzweigtes C<sub>1</sub>-C<sub>4</sub>-Alkyl steht, welches optional mit OH oder O-methyl endsubstituiert ist.

3. Verbindung nach Anspruch 1 oder 2, wobei R<sup>1</sup> für Ethyl, n-Propyl oder Cyclopentyl, Pyrimidin-2-yl oder -CH<sub>2</sub>-(pyridin-2-yl) steht.

4. Verbindung nach einem der voranstehenden Ansprüche, wobei R<sup>2</sup> für Methyl, Hydroxymethyl, Ethyl, Propyl oder Cyclopropylmethyl, -CH<sub>2</sub>-(pyridin-2-yl), -CH<sub>2</sub>-(pyrimidin-2-yl), -CH<sub>2</sub>-(morpholinyl), -CH<sub>2</sub>-(pyrazin-2-yl), Benzyl, -CH<sub>2</sub>OCH<sub>2</sub>-phenyl, Phenyl oder Pyrazin-2-yl steht.

5. Verbindung nach einem der voranstehenden Ansprüche, wobei R<sup>3</sup> für lineares oder verzweigtes C<sub>2</sub>-C<sub>3</sub>-Alkyl steht, welches optional mit OCH<sub>3</sub> endsubstituiert ist.

6. Verbindung nach einem der voranstehenden Ansprüche, wobei R<sup>12</sup> und R<sup>13</sup> zusammen mit dem Stickstoffatom, an welches sie gebunden sind, 4-R<sup>14</sup>-Piperazinyl bedeuten, wobei R<sup>14</sup> C<sub>1</sub>-C<sub>3</sub>-Alkyl bedeutet, welches optional mit OH endsubstituiert ist.

7. Verbindung nach einem der Ansprüche 1 bis 6 zur Verwendung als Arzneimittel.

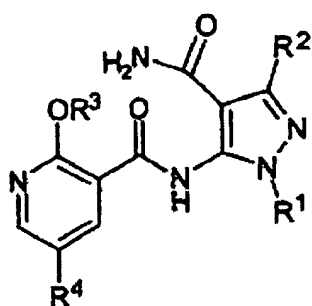
8. Verbindung nach einem der Ansprüche 1 bis 6 zur Verwendung als Tiermedikament.

9. Formulierung, umfassend eine Verbindung nach einem der Ansprüche 1 bis 6 im Gemisch mit einem pharmazeutisch oder veterinärmedizinisch akzeptablen Adjuvans, Verdünnungsmittel oder Träger.

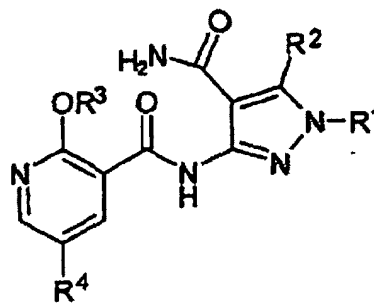
10. Formulierung nach Anspruch 9, welche eine pharmazeutische Formulierung ist.

11. Formulierung nach Anspruch 9, welche eine veterinärmedizinische Formulierung ist.
12. Verwendung einer Verbindung wie in einem der Ansprüche 1 bis 6 definiert bei der Herstellung eines Medikaments für die Therapie oder Prophylaxe eines medizinischen Zustandes, bei welchem Inhibierung von cGMP PDE5 erwünscht ist.
13. Verwendung nach Anspruch 12, wobei der medizinische Zustand Erektionsdysfunktion beim Mann, sexuelle Dysfunktion bei der Frau, vorzeitige Wehen, Dysmenorrhoe, gutartiger Prostatakrebs (BPH), Blasenaußlaßversperung, Inkontinenz, Angina der stabilen oder instabilen Variante (Prinzmetal-Angina), Hypertonie, Lungenhypertonie, kongestive Herzinsuffizienz, Atherosklerose, Schlaganfall, periphere Gefäßerkrankung, Zustände verringerter Blutgefäßöffnung, chronisches Asthma, Bronchitis, allergisches Asthma, allergischer Schnupfen, Glaucoma, eine Krankheit **gekennzeichnet durch** Störungen der Darmmotilität, Präeklampsie, Kawasaki's Syndrom, Nitrat-Toleranz, multiple Sklerose, periphere diabetische Neuropathie, Alzheimer-Krankheit, akute respiratorische Insuffizienz, Psoriasis, Hautnekrose, Krebsmetastase oder Kahlheit ist.
14. Verfahren zur Herstellung einer Verbindung der Formel IA oder der Formel IB, wie in Anspruch 1 definiert, welches umfasst:

(a) Cyclisierung einer entsprechenden Verbindung der Formel IIA bzw. der Formel IIB:



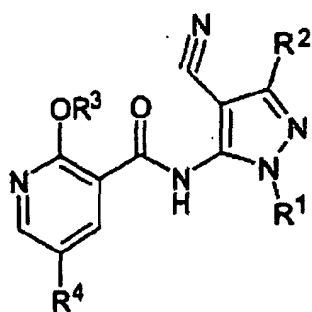
IIA



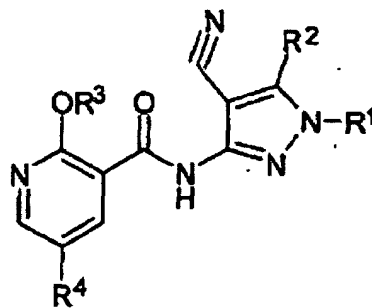
IIB

wobei R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> wie in Anspruch 1 definiert sind;

b) Cyclisierung einer entsprechenden Verbindung der Formel VA bzw. der Formel VB:



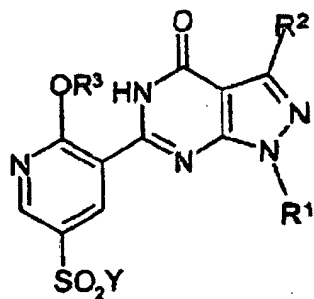
VA



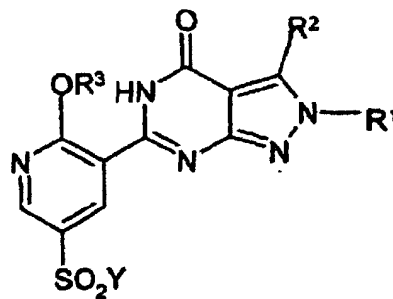
VB

wobei R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> wie in Anspruch 1 definiert sind;

(c) Reaktion einer entsprechenden Verbindung der Formel VIIA bzw. der Formel VIIB:

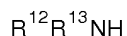


VIIA



VIIB

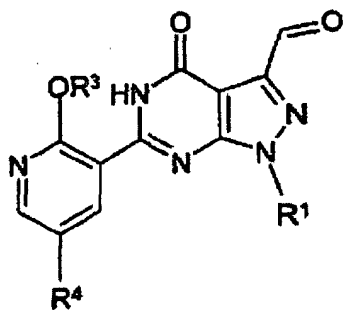
wobei Y Halogen ist und R¹, R² und R³ wie in Anspruch 1 definiert sind, mit einer Verbindung der Formel VIII:



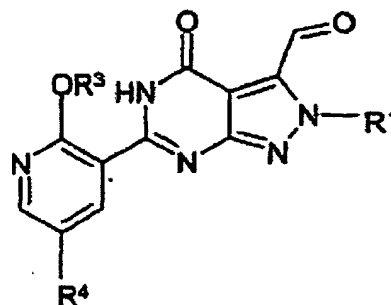
VIII

wobei R¹² und R¹³ wie in Anspruch 1 definiert sind;

(d) für Verbindungen der Formeln IA und IB, in welchen R² C₁-C₄-Alkyl, C₁-C₃-AlkylHet oder C₁-C₃-Alkylaryl bedeutet, Reaktion einer entsprechenden Verbindung der Formel XVIA bzw. der Formel XVIB:



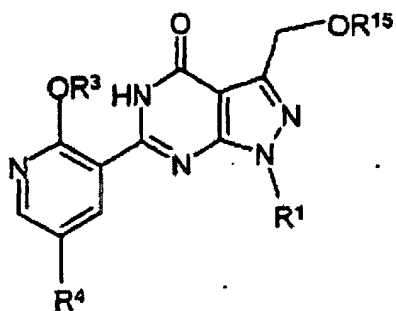
XVIA



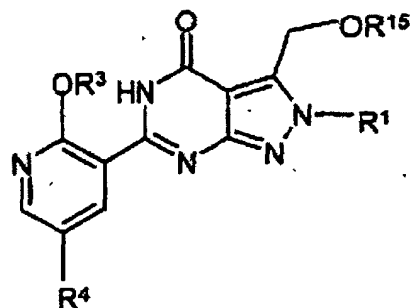
XVIB

wobei R¹, R³ und R⁴ wie in Anspruch 1 definiert sind, mit entweder einer organometallischen Verbindung der Formel R²ᵃM, wobei M für Li oder MgHal steht, wobei Hal Halogen bedeutet und R²ᵃ eine Gruppe bedeutet, welche die relevante R²-Gruppe bereitstellt bei Reaktion mit der -C=O-Gruppe, welche an den Pyrazolring gebunden ist, gefolgt von Deoxygenierung des resultierenden sekundären Alkohols, oder durch reduktive Aminierung unter Verwendung einer basischen Verbindung, welche bei Reaktion mit der an den Pyrazolring gebundenen -C=O-Gruppe eine R²-Gruppe bereitstellt;

(e) für Verbindungen der Formeln IA und IB, in welchen R² CH₂OH bedeutet, Schutzgruppenentfernung von einer entsprechenden Verbindung der Formel XVIIA bzw. der Formel XVIIB:



XVIIA



XVIIIB

wobei R<sup>1</sup>, R<sup>3</sup> und R<sup>4</sup> wie in Anspruch 1 definiert sind und R<sup>15</sup> für eine Alkohol-Schutzgruppe steht;

(f) für Verbindungen der Formel IA oder IB, in welchen R<sup>1</sup> C<sub>2</sub>-C<sub>5</sub>-Alkyl oder C<sub>1</sub>-C<sub>3</sub>-Alkylhet bedeutet, Alkylierung einer entsprechenden Verbindung der Formel IA bzw. IB, in welchen R<sup>1</sup> H bedeutet;

(g) Umwandlung, Entfernung oder Einführung eines Substituenten an einer Aryl-, oder einer Het-Gruppe in oder an der Pyridinyl- oder Pyrazolo-Einheit einer Verbindung der Formel IA oder IB;

(h) Umwandlung einer R<sup>3</sup>-Gruppe in eine andere durch Alkoxid-Austausch;

(i) für Verbindungen der Formel IA oder IB, in welchen R<sup>12</sup> und R<sup>13</sup> zusammen mit dem Stickstoff, an welchen sie gebunden sind, eine 4-R<sup>14</sup>-Piperazinyl-Gruppe bilden, in welcher R<sup>14</sup> C<sub>1</sub>-C<sub>6</sub>-Alkyl bedeutet, Alkylierung einer entsprechenden Verbindung der Formel IA oder IB, in welchen R<sup>14</sup> Wasserstoff bedeutet; oder

(j) Schutzgruppenentfernung von einem geschützten Derivat einer Verbindung der Formel IA oder der Formel IB.

15. Verbindung der Formel IIA oder Formel IIB, wie in Anspruch 14 definiert.

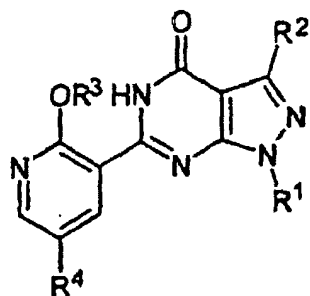
16. Verbindung der Formel VA oder Formel VB, wie in Anspruch 14 definiert.

17. Verbindung der Formel VIIA oder Formel VIIB, wie in Anspruch 14 definiert.

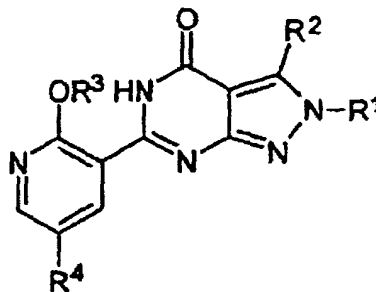
18. Verbindung der Formel XVIA oder Formel XVIB, wie in Anspruch 14 definiert.

## Revendications

1. Composé de formule IA, ou de formule IB :



IA



IB

dans laquelle

R<sup>1</sup> représente un groupe alkyle en C<sub>2</sub> à C<sub>5</sub> linéaire ou cyclique, Het ou (alkyle en C<sub>1</sub> à C<sub>3</sub>) Het, dans lesquels, dans les deux derniers cas, Het représente un noyau aromatique hexagonal contenant un ou deux atomes d'azote ;

R<sup>2</sup> représente un groupe alkyle en C<sub>1</sub> à C<sub>4</sub> linéaire ou ramifié, cyclique, acyclique ou partiellement cyclique (groupe alkyle qui est facultativement terminé avec un groupe OH), (alkyle en C<sub>1</sub> à C<sub>3</sub>) Het (dans lequel Het représente un groupe hétérocyclique hexagonal contenant un ou deux atomes d'azote), (alkyle en C<sub>1</sub> à C<sub>3</sub>) aryle (dont le groupe alkyle est facultativement interrompu par un atome de O), aryle ou Het (Het représentant un groupe hétérocyclique hexagonal contenant un ou deux atomes d'azote) ;

R<sup>3</sup> représente un groupe alkyle en C<sub>1</sub> à C<sub>6</sub> linéaire ou ramifié, facultativement terminé par un groupe OH ou O-méthyle ;

R<sup>4</sup> représente un groupe SO<sub>2</sub>NR<sup>12</sup>R<sup>13</sup> ;

R<sup>12</sup> et R<sup>13</sup>, conjointement avec l'atome d'azote auquel ils sont fixés, représentent un groupe 4-R<sup>14</sup>-pipérazinyle, dans lequel R<sup>14</sup> représente un groupe alkyle en C<sub>1</sub> à C<sub>6</sub>, facultativement terminé par un groupe OH ; et

R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10a</sup>, R<sup>10b</sup>, R<sup>11a</sup> et R<sup>11b</sup> représentent indépendamment H ou un groupe alkyle en C<sub>1</sub> à C<sub>6</sub> ; et

le terme « aryle » désigne un groupe aromatique carbocyclique hexa- à décagonal, groupe qui est facultativement substitué avec un ou plusieurs substituants choisis entre des substituants aryle, alkyle en C<sub>1</sub> à C<sub>6</sub>, Het, halogéno, cyano, nitro, OR<sup>5</sup>, C(O)R<sup>6</sup>, C(O)OR<sup>7</sup>, C(O)NR<sup>8</sup>R<sup>9</sup>, NR<sup>10a</sup>R<sup>10b</sup>, SO<sub>2</sub>NR<sup>11a</sup>R<sup>11b</sup> et N(H)SO<sub>2</sub>R<sup>11a</sup> ;

ou un de ses sels ou produits de solvatation acceptables du point de vue pharmaceutique ou vétérinaire.

2. Composé suivant la revendication 1, dans lequel R<sup>3</sup> représente un groupe alkyle en C<sub>1</sub> à C<sub>4</sub> linéaire ou ramifié, facultativement terminé par un groupe OH ou O-méthyle.

3. Composé suivant la revendication 1 ou la revendication 2, dans lequel R<sup>1</sup> représente un groupe éthyle, n-propyle ou cyclopentyle, pyrimidine-2-yle ou -CH<sub>2</sub>-(pyridine-2-yle).

4. Composé suivant l'une quelconque des revendications précédentes, dans lequel R<sup>2</sup> représente un groupe méthyle, hydroxyméthyle, éthyle, propyle ou cyclopropylméthyle, -CH<sub>2</sub>-(pyridine-2-yle), -CH<sub>2</sub>-(pyrimidine-2-yle), -CH<sub>2</sub>-(morpholinyle), -CH<sub>2</sub>-(pyrazine-2-yle), benzyle, -CH<sub>2</sub>OCH<sub>2</sub>-phényle, phényle ou pyrazine-2-yle.

5. Composé suivant l'une quelconque des revendications précédentes, dans lequel R<sup>3</sup> représente un groupe alkyle en C<sub>2</sub> ou C<sub>3</sub> linéaire ou ramifié, facultativement terminé par un groupe OCH<sub>3</sub>.

6. Composé suivant l'une quelconque des revendications précédentes, dans lequel R<sup>12</sup> et R<sup>13</sup>, conjointement avec l'atome d'azote auquel ils sont fixés, représentent un groupe 4-R<sup>14</sup>-pipérazinyle, dans lequel R<sup>14</sup> représente un groupe alkyle en C<sub>1</sub> à C<sub>3</sub> facultativement terminé par un groupe OH.

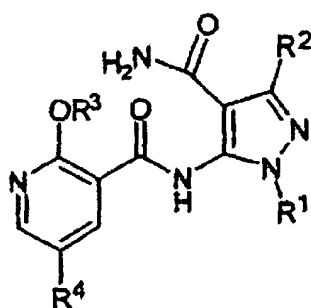
7. Composé tel que défini dans l'une quelconque des revendications 1 à 6, destiné à être utilisé comme agent pharmaceutique.

8. Composé tel que défini dans l'une quelconque des revendications 1 à 6, destiné à être utilisé comme médicament pour animaux.

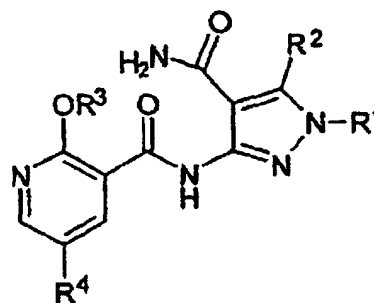


9. Formulation comprenant un composé tel que défini dans l'une quelconque des revendications 1 à 6, en mélange avec un adjuvant, diluant ou support acceptable du point de vue pharmaceutique ou vétérinaire.
10. Formulation suivant la revendication 9, qui est une formulation pharmaceutique.
11. Formulation suivant la revendication 9, qui est une formulation vétérinaire.
12. Utilisation d'un composé tel que défini dans l'une quelconque des revendications 1 à 6 dans la production d'un médicament pour le traitement curatif ou prophylactique d'un état médical pour lequel une inhibition de cGMP PDE5 est désirée.
13. Utilisation suivant la revendication 12, dans laquelle l'état est un dysfonctionnement de l'érection masculine, un dysfonctionnement sexuel féminin, un accouchement prématuré, la dysménorrhée, l'hyperplasie prostatique bénigne (BPH), une obstruction de la sortie de la vessie, l'incontinence, l'angor variant (de Prinzmetal) stable ou instable, l'hypertension, l'hypertension pulmonaire, l'insuffisance cardiaque congestive, l'athérosclérose, un ictus, une maladie vasculaire périphérique, des états de patence réduite des vaisseaux sanguins, l'asthme chronique, la bronchite, l'asthme allergique, la rhinite allergique, le glaucome, une maladie **caractérisée par** des troubles de la motilité intestinale, la prééclampsie, le syndrome de Kawasaki, la tolérance vis-à-vis des nitrates, la sclérose en plaques, la neuropathie diabétique périphérique, un ictus, la maladie d'Alzheimer, l'insuffisance respiratoire aiguë, le psoriasis, la nécrose cutanée, la métastase d'un cancer ou la calvitie.
14. Procédé pour la préparation d'un composé de formule IA, ou de formule IB, telle que définie dans la revendication 1, qui comprend :

(a) la cyclisation d'un composé correspondant de formule IIA, ou de formule IIB, respectivement :

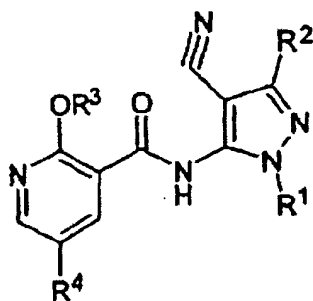


IIA

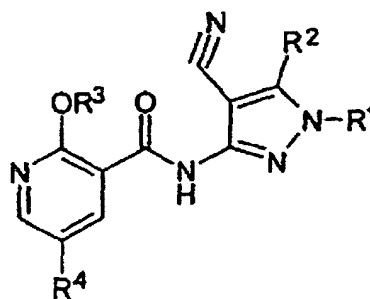


IIB

dans laquelle R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> sont tels que définis dans la revendication 1 ;  
 (b) la cyclisation d'un composé correspondant de formule VA, ou de formule VB, respectivement :

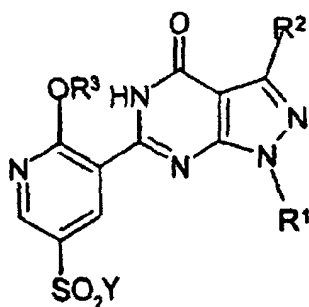


VA

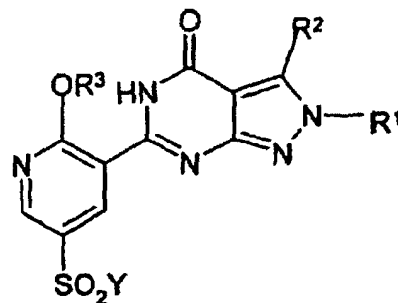


VB

dans laquelle  $R^1$ ,  $R^2$ ,  $R^3$  et  $R^4$  sont tels que définis dans la revendication 1 ;  
 (c) la réaction d'un composé correspondant de formule VIIA, ou de formule VIIB, respectivement :



VIIA

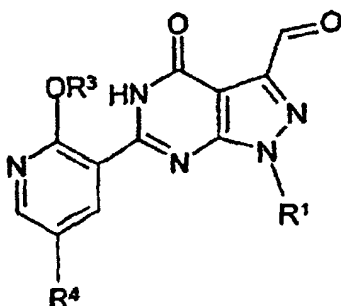


VIIB

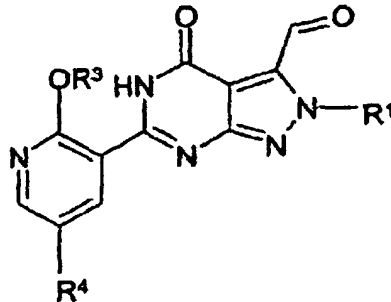
dans laquelle Y représente un groupe halogéno et  $R^1$ ,  $R^2$  et  $R^3$  répondent aux définitions figurant dans la revendication 1, avec un composé de formule VIII :



dans laquelle  $R^{12}$  et  $R^{13}$  sont tels que définis dans la revendication 1 ;  
 (d) pour des composés de formule IA et IB, dans lesquelles  $R^2$  représente un groupe alkyle en  $C_1$  à  $C_4$ , (alkyle en  $C_1$  à  $C_3$ ) Het ou (alkyle en  $C_1$  à  $C_3$ ) aryle, la réaction d'un composé correspondant de formule XVIA, ou de formule XVIB, respectivement :

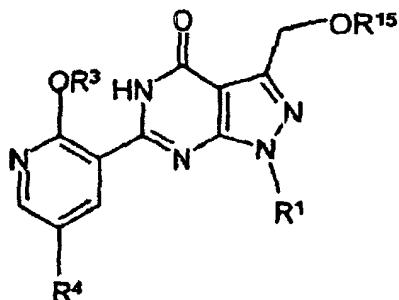


XVIA

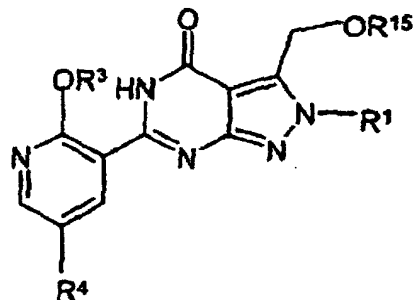


XVIB

dans laquelle  $R^1$ ,  $R^3$  et  $R^4$  sont tels que définis dans la revendication 1, avec un composé organométallique de formule  $R^{2a}M$ , dans laquelle M représente Li ou  $MgHal$ , dans lequel Hal représente un groupe halogéno, et  $R^{2a}$  représente un groupe qui fournit le groupe  $R^2$  correspondant par réaction avec le groupe  $-C=O$  qui est fixé au noyau pyrazole, avec ensuite une désoxygénation de l'alcool secondaire résultant, ou par amination réductrice en utilisant un composé basique qui fournit un groupe  $R^2$  par réaction avec le groupe  $-C=O$  qui est fixé au noyau pyrazole ;  
 (e) pour des composés de formules IA et IB dans lesquelles  $R^2$  représente un groupe  $CH_2OH$ , la suppression de la protection d'un composé correspondant de formule XVIA, ou de formule XVIB, respectivement :



XVIIA



XVIIIB

dans laquelle  $R^1$ ,  $R^3$  et  $R^4$  sont tels que définis dans la revendication 1 et  $R^{15}$  représente un groupe protecteur de la fonction alcool ;

(f) pour des composés de formule IA ou IB dans laquelle  $R^1$  représente un groupe alkyle en  $C_2$  à  $C_5$ , ou (alkyle en  $C_1$  à  $C_3$ ) Het, l'alkylation d'un composé correspondant de formule IA, ou de formule IB, respectivement, dans laquelle  $R^1$  représente H ;

(g) la conversion, l'élimination ou l'introduction d'un substituant sur un groupe aryle, ou un groupe Het, dans ou sur le motif pyridinyle, ou pyrazolo, d'un composé de formule IA ou IB ;

(h) la conversion d'un groupe  $R^3$  en un autre par échange d'alcoolate ;

(i) pour des composés de formule IA ou IB, dans laquelle  $R^{12}$  et  $R^{13}$ , conjointement avec l'atome d'azote auquel ils sont fixés, forment un groupe 4- $R^{14}$ -pipérazinyle dans lequel  $R^{14}$  représente un groupe alkyle en  $C_1$  à  $C_6$ , l'alkylation d'un composé correspondant de formule IA ou IB dans laquelle  $R^{14}$  représente un atome d'hydrogène ; ou

(j) la suppression de la protection d'un dérivé protégé d'un composé de formule IA ou de formule IB.

15. Composé de formule IIA, ou de formule IIB, tel que défini dans la revendication 14.

16. Composé de formule VA, ou de formule VB, tel que défini dans la revendication 14.

17. Composé de formule VIIA, ou de formule VIIB, tel que défini dans la revendication 14.

18. Composé de formule XVIA, ou de formule XVIB, tel que défini dans la revendication 14.